Supporting Information

γ-Lactam Synthesis from Cyclobutanone with Oximes *via* Transoximaiton and Beckmann Rearrangement

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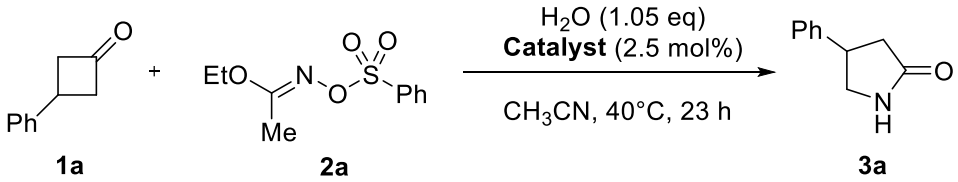
Content

1. General Information

All reactions were performed in oven-dried glassware under a positive pressure of nitrogen. Solvents were transferred via syringe and were introduced into the reaction vessels through a rubber septum. All reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm Merck silica-gel (60-F254). The TLC plates were visualized with UV light and basic $KMnO_4$ in H_2O/heat. Column chromatography was carried out on a column packed with silica-gel 60N spherical neutral size 40-50 μm. Distillation was performed under reduced pressure. ^1H NMR (400 MHz), ^{13}C NMR (100 MHz), ^{19}F NMR (376 MHz) and ^{31}P NMR (162 MHz) spectra for solution in $CDCl_3$ were recorded on a JEOL RESONANCE JNM-ECS-400. Chemical shifts (δ) are expressed in ppm downfield from internal TMS or $CHCl_3$ or C_6F_6 or H_3PO_4. ESI-MS were recorded on a JEOL AccuTOF LC- plus 4G system with 1260 Infinity HPLC or Thermo Scientific Exactive Plus. Melting points were recorded on a Yanaco MICRO MELTING POINT APPARATUS. Cyclic ketones were synthesized by referring previous literatures.[1, 2)] Oxime reagents **2a**-**2d** were prepared following previous reports.[3, 4)] Other reagents and solvents not listed here are commercially available.

2. Synthetic Procedures for *γ*-Lactam

Table S1. Screening of various acid catalysts [a)]

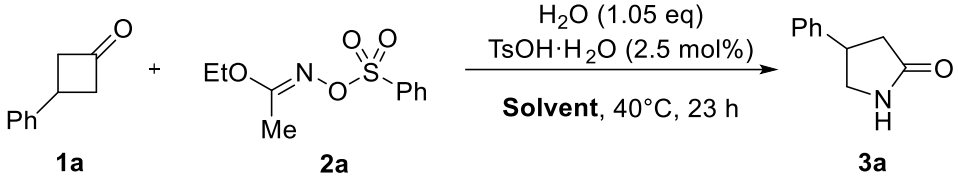


1a **2a** **3a**

Entry	Catalyst	Yield (%)[b)]
1	$TsOH·H_2O$	75
2	AcOH	-
3	CF_3COOH	40
4	HCl	52
5	H_2SO_4	72
6	MsOH	52
7	$Cu(OTf)_2$	66
8	AgOTf	-
9	$Mg(OTf)_2$	-

a) Reaction conditions: **1a** (0.50 mmol), **2a** (0.60 mmol, 1.2 eq), Catalysts (0.0125 mmol, 2.5 mol%), H_2O (0.525 mmol, 1.05 eq) in CH_3CN at 40 ºC for 23 h. b) Isolated yield.

Table S2. Screening of various solvents [a)]



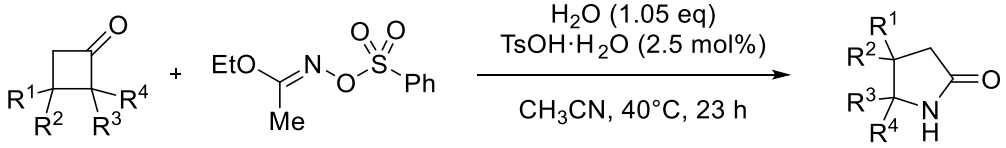
1a **2a** **3a**

Entry	Catalyst	Yield (%)[b)]
1	CH_3CN	75
2	$ClCH_2CH_2Cl$	51
3	Hexane	27
4	THF	34
5	Dioxane	26
6	DMSO	-
7	DMF	-
8	Toluene	53
9	H_2O	-

a) Reaction conditions: **1a** (0.50 mmol), **2a** (0.60 mmol, 1.2 eq), Catalysts (0.0125 mmol, 2.5 mol%), H_2O (0.525 mmol, 1.05 eq) in CH_3CN at 40 ºC for 23 h. b) Isolated yield.

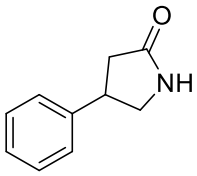
3. Synthetic Procedures for *γ*-Lactam

General procedure for direct synthesis of *γ*-Lactam from cyclic ketones



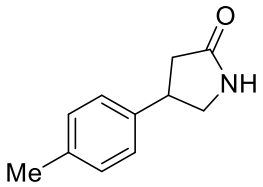
To a test tube was added cyclobutanone (0.500 mmol, 1.0 eq), oxime (0.600 mmol, 1.2eq), TsOH·H_2O (0.0125 mmol, 2.5 mol%), acetonitrile (1.0 M) under N_2 at 40°C. After indicated time, the reaction mixture was quenched by sat. $NaHCO_3$ (3 mL) and work up with ethyl acetate (10 ml × 3). The combined organic phase was washed with brine and dried over Na_2SO_4. After removal of Na_2SO_4 by filtration, the collected solution was evaporated under reduced pressure and the remained crude mixture was purified by silica gel column chromatography (ethyl acetate/methanol = 98/2).

4-phenyl-pyrrolidin-2-one (3a) [5)]



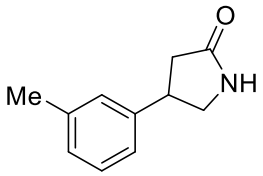
White solid (62.8 mg, 78%, 0.500 mmol scale, column eluent: ethyl acetate/methanol = 99/1); mp 72-74 ºC (73-75 ºC) [6)]; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.35 (d, J = 8.0 Hz, 2H), 7.27 (t, J = 7.6 Hz, 3H), 6.94 (s, 1H), 3.79 (t, J = 8.4 Hz, 1H), 3.70 (quin, J = 8.0 Hz, 1H), 3.43 (dd, J = 7.6 Hz, 1H), 2.74 (q, J = 7.6 Hz, 1H), 2.51 (q, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 178.0, 142.2, 128.9, 127.2, 126.9, 49.7, 40.4, 38.1; HRMS *m*/*z* (ESI, positive) calcd for $C_{10}H_{12}NO^+$ $[M+H]^+$: 162.0913, Found 162.0913.

4-(*p*-tolyl)pyrrolidin-2-one (3b) [5)]



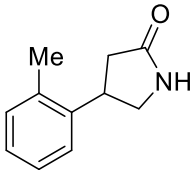
White solid (67.2 mg, 77%, 0.500 mmol scale using 5 mol% TsOH, column eluent: ethyl acetate/methanol = 98/2); mp 88-92 ºC (137-139 ºC) [6)]; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.16 (s, 4H), 5.77 (s, 1H), 3.76 (t, J = 8.8 Hz, 1H), 3.68 (quint, J = 8.4 Hz, 1H), 3.40 (dd, J = 8.8, 7.2 Hz, 1H), 2.72 (dd, J = 16.8, 8.8 Hz, 1H), 2.49 (dd, J = 16.8, 8.8 Hz, 1H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 207.3, 140.7, 136.4, 129.5, 126.5, 54.9, 28.2, 21.1;HRMS *m*/*z* (ESI, positive) calcd for $C_{11}H_{13}NNaO^+$ $[M+Na]^+$: 198.0895, Found 198.0890.

4-(*m*-tolyl)pyrrolidin-2-one (3c) [8)]



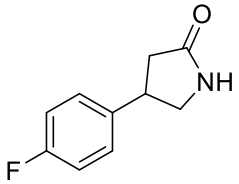
White solid (73.8 mg, 84%, 0.500 mmol scale, column eluent: ethyl acetate/methanol = 98/2); mp 102-105 ºC; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.24 (t, J = 8.0 Hz, 1H), 7.07 (t, J = 8.8 Hz, 3H), 6.25 (s, 1H), 3.80-3.75 (m, 1H), 3.66 (quint, J = 8.4 Hz, 1H), 3.42 (dd, J = 9.6, 7.2 Hz, 1H), 2.72 (dd, J = 16.8, 8.8 Hz, 1H), 2.51 (dd, J = 16.8, 8.8 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 177.9, 142.2, 138.7, 128.9, 128.0, 127.7, 123.9, 49.7, 40.4, 38.1, 21.6; HRMS *m*/*z* (ESI, positive) calcd for $C_{11}H_{13}NNaO^+$ $[M+Na]^+$: 198.0895, Found 198.0889.

4-(*o*-tolyl)pyrrolidin-2-one (3d)



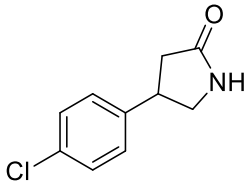
White solid (61.8 mg, 71%, 0.500 mmol scale, column eluent: ethyl acetate/methanol = 98/2); mp 106-109 ºC; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.28 (d, J = 7.2 Hz, 1H), 7.24-7.14 (m, 3H), 6.35 (s, 1H), 3.91 (quint, J = 8.0 Hz, 1H), 3.77 (t, J = 8.8 Hz, 1H), 3.41 (dd, J = 9.6, 6.4 Hz, 1H), 2.73 (dd, J = 16.8, 8.8 Hz, 1H), 2.48 (dd, J = 16.8, 8.8 Hz, 1H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 177.8, 140.4, 135.8, 130.8, 127.0, 126.8, 125.4, 48.9, 37.5, 36.2, 19.9; HRMS *m*/*z* (ESI, positive) calcd for $C_{11}H_{13}NNaO^+$ $[M+Na]^+$: 198.0895, Found 198.0890.

4-(4-fluorophenyl)pyrrolidin-2-one (3e) [5)]



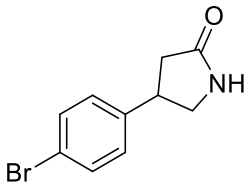
White solid (62.8 mg, 70%, 0.500 mmol scale, column eluent: ethyl acetate/methanol = 99/1); mp 95-97 ºC (98-99 ºC) [7)]; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.25-7.21 (m, 2H), 7.08-7.01 (m, 2H), 6.59 (s, 1H), 3.79 (t, J = 8.4 Hz, 1H), 3.69 (quin, J = 8.8 Hz, 1H), 3.39 (dd, J = 9.6, 7.2 Hz, 1H), 2.74 (dd, J = 16.8, 8.8 Hz, 1H), 2.46 (dd, J = 16.8, 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 177.7, 162.0 (q, J = 245 Hz), 137.9 (q, J = 3 Hz), 128.4 (q, J = 8 Hz), 115.8 (q, J = 21 Hz), 49.8, 39.7, 38.2; ^{19}F NMR (376 MHz, $CDCl_3$, ppm) δ -118.7; HRMS *m*/*z* (ESI, positive) calcd for $C_{10}H_{10}FNNaO^+$ $[M+Na]^+$: 202.0644, Found 202.0638.

4-(4-chlorophenyl)pyrrolidin-2-one (3f) [5]



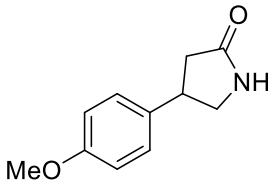
White solid (69.0 mg, 71%, 0.500 mmol scale, column eluent: ethyl acetate/methanol = 99/1); mp 110-113 ºC (115-117 ºC) [7]; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.32 (dt, J = 9.2, 2.4 Hz, 2H), 7.19 (dt, J = 8.8, 2.4 Hz, 2H), 6.01 (s, 1H), 3.79 (td, J = 8.8, 0.8 Hz, 1H), 3.68 (quin, J = 8.4 Hz, 1H), 3.38 (dd, J = 9.6, 7.2 Hz, 1H), 2.74 (q, J = 8.4 Hz, 1H), 2.46 (q, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 177.9, 140.8, 132.9, 129.0, 128.2, 49.6, 39.7, 38.1; HRMS *m*/*z* (ESI, positive) calcd for $C_{10}H_{10}ClNNaO^+$ $[M+Na]^+$: 218.0349, Found 218.0343.

4-(4-bromophenyl)pyrrolidin-2-one (3g)



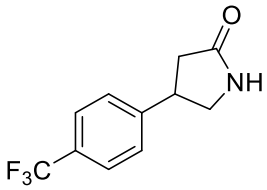
White solid (91.9 mg, 77%, 0.500 mmol scale, column eluent: ethyl acetate/methanol = 99/1); mp 123-126 ºC; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.47 (dt, J = 9.2, 2.4 Hz, 2H), 7.14 (dt, J = 8.8, 2.4 Hz, 2H), 5.91 (s, 1H), 3.79 (td, J = 8.8, 1.2 Hz, 1H), 3.67 (quin, J = 8.4 Hz, 1H), 3.38 (dd, J = 9.6, 7.2 Hz, 1H), 2.74 (dd, J = 16.8, 8.8 Hz, 1H), 2.45 (dd, J = 16.8, 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 177.5, 141.3, 132.1, 128.6, 121.0, 49.4, 39.9, 37.9; HRMS *m*/*z* (ESI, positive) calcd for $C_{10}H_{10}BrNNaO^+$ $[M+Na]^+$: 261.9843, Found 261.9839.

4-(4-methoxyphenyl)pyrrolidin-2-one (3h) [9]



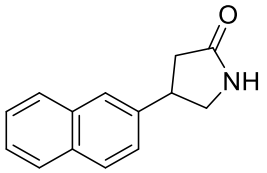
White solid (70.5 mg, 74%, 0.500 mmol scale, column eluent: ethyl acetate/methanol = 99/1); mp 125-127 ºC (121-123 ºC) [7]; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.18 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 5.68 (br, 1H), 3.80 (s, 3H), 3.75 (dd, J = 9.2, 8.4 Hz, 1H), 3.70-3.62 (m, 1H), 3.38 (dd, J = 9.2, 7.2 Hz, 1H), 2.71 (dd J = 8.8, 8.8 Hz, 1H), 2.47 (dd, J = 9.2, 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 178.2, 158.6, 134.2, 127.8, 114.2, 55.3, 49.9, 39.7 38.3; HRMS *m*/*z* (ESI, positive) calcd for $C_{11}H_{14}NO_2^+$ $[M+H]^+$: 192.1019, Found 192.1015.

4-(4-(trifluoromethyl)phenyl)pyrrolidin-2-one (3i) [5)]



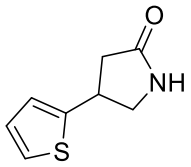
White solid (85.6 mg, 75%, 0.500 mmol scale, column eluent: ethyl acetate/methanol = 98/2); mp 116-118 ºC; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.61 (d, J = 8.0 Hz, 2H), 7.39 (d, J = 8.0 Hz, 2H), 7.07, (s, 1H), 3.87-3.73 (m, 2H), 3.46-3.42 (m, 1H), 2.79 (dd, J = 16.8, 8.8 Hz, 1H), 2.50 (dd, J = 16.8, 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 177.7, 146.4, 129.6 (q, J = 32 Hz), 127.3, 125.8, 124.1(q, J = 271 Hz) 49.4, 40.1, 38.0; ^{19}F NMR (376 MHz, $CDCl_3$, ppm) δ -65.8; HRMS m/z (ESI, positive) calcd for $C_{11}H_{10}F_3NNaO^+$ $[M+Na]^+$: 252.0612, Found 252.0606.

4-(naphthalen-2-yl)pyrrolidin-2-one (3j) [5)]



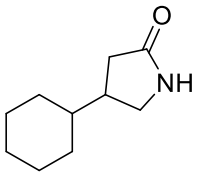
White solid (873 mg, 81%, 5.10 mmol scale, column eluent: ethyl acetate/methanol = 98/2); mp 137-140 ºC; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.86-7.80 (m, 3H), 7.69 (s, 1H), 7.52-7.45 (m, 2H), 7.39 (dd, J = 8.4, 2.0 Hz, 1H), 5.69 (s, 1H), 3.93-3.84 (m, 2H), 3.56-3.50 (m, 1H), 2.82 (dd, J = 16.8, 8.8 Hz, 1H), 2.63 (dd, J = 16.8, 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 177.7, 139.5, 133.5, 132.6, 128.9, 127.8, 126.6, 126.1, 125.5, 125.0, 49.5, 40.5, 37.9; HRMS m/z (ESI, positive) calcd for $C_{14}H_{13}NNaO^+$ $[M+Na]^+$: 234.0895, Found 234.0890.

4-(2-thienyl)pyrrolidin-2-one (3k) [10)]



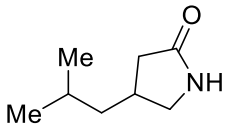
White solid (61.8 mg, 74%, 0.500 mmol scale, column eluent: ethyl acetate/methanol = 99/1); mp 80-82 ºC; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.21-7.20 (m, 1H), 6.97 (dd, J = 3.6, 3.2 Hz, 1H), 6.91 (m, 1H), 5.97 (br, 1H), 3.97 (quin, J = 8.4 Hz, 1H), 3.82-3.78 (m, 1H), 3.47 (dd, J = 8.0, 8.0 Hz, 1H), 2.78 (dd, J = 8.4, 8.8 Hz, 1H), 2.54 (dd, J = 8.4, 9.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 177.3, 145.3, 127.1, 124.1, 124.0, 50.2, 39.1, 36.2; HRMS m/z (ESI, positive) calcd for $C_8H_{10}NOS^+$ $[M+H]^+$: 168.0478, Found 168.0476.

4-cyclohexyl-pyrrolidin-2-one (3l) [5)]



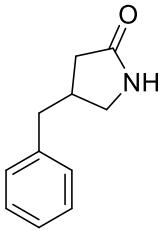
White solid (60.0 mg, 72%, 0.500 mmol scale, column eluent: ethyl acetate/methanol = 99/1); mp 108-111 ºC; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 5.77 (br, 1H), 3.44 (t, J = 8.4 Hz, 1H), 3.08 (t, J = 9.2 Hz, 1H), 2.36 (quin, J = 8.0 Hz, 1H), 2.28-2.17 (m, 1H), 2.05 (q, J = 6.4 Hz, 1H), 1.76-1.64 (m, 5H), 1.31-1.10 (m, 4H), 1.00-0.88 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 178.7, 46.6, 42.3, 41.4, 35.1, 31.3, 30.7, 26.4, 26.1, 26.0; HRMS *m*/*z* (ESI, positive) calcd for $C_{10}H_{18}NO^+$ $[M+H]^+$: 168.1383, Found 168.1385.

Pregabalin lactam (3m) [11)]



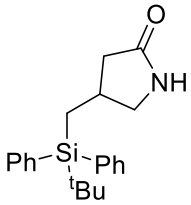
Colorless liquid (51.8 mg, 73%, 0.500 mmol scale, column eluent: ethyl acetate/methanol = 98/2); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 5.98 (s, 1H), 3.48 (td, J = 8.6, 1.6 Hz, 1H), 3.00 (dd, J = 9.6, 7.2 Hz, 1H), 2.55 (sep, J = 8.0 Hz, 1H), 2.42 (dd, J = 16.8, 8.4 Hz, 1H), 1.99 (dd, J = 16.8, 8.4 Hz, 1H), 1.58 (sep, J = 6.8 Hz, 1H), 1.36 (td, J = 7.2, 2.4 Hz, 2H), 0.91 (dd, J = 6.4, 4.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 178.5, 48.3, 44.0, 37.0, 33.2, 26.3, 22.8, 22.7; HRMS *m*/*z* (ESI, positive) calcd for $C_8H_{16}NO^+$ $[M+H]^+$: 142.1232, Found 142.1226.

4-benzyl-pyrrolidin-2-one (3n) [12)]



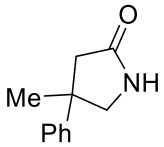
White solid (59.0 mg, 67%, 0.500 mmol scale, column eluent: ethyl acetate/methanol = 98/2); mp 97-102 ºC; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.32-7.15 (m, 5H), 6.24 (br, 1H), 3.41 (d, J = 9.2 Hz, 1H), 3.11 (d, J = 9.2 Hz, 1H), 2.79-2.71 (m, 3H), 2.40 (d, J = 7.6 Hz, 1H), 2.12 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 178.2, 139.4, 128.8, 128.7, 126.6, 47.5, 40.5, 36.6, 36.5; HRMS *m*/*z* (ESI, positive) calcd for $C_{11}H_{13}NNaO^+$ $[M+Na]^+$: 198.0895, Found 198.0890.

4-((*tert*-butyldiphenylsilyl)methyl)pyrrolidin-2-one (3o)



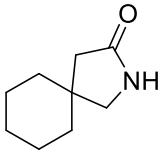
White solid (104 mg, 62%, 0.500 mmol scale, column eluent: ethyl acetate/methanol = 98/2); mp 129-133 ºC; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.61 (dd, J = 8.0, 1.6 Hz, 4H), 7.44-7.35 (m, 6H), 5.55 (s, 1H), 3.04 (dd, J = 9.2, 7.6 Hz, 1H), 2.76 (t, J = 8.8 Hz, 1H), 2.50 (quint, J = 7.6 Hz, 1H), 2.07 (dd, J = 16.8, 8.0 Hz, 1H), 1.82 (dd, J = 16.4, 9.2 Hz, 1H), 1.38 (d, J = 7.6 Hz, 2H), 1.03 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 178.2, 136.1, 136.1, 134.3, 134.0, 129.6, 129.6, 128.0, 127.9, 50.6, 39.8, 32.1, 27.9, 18.2, 15.9; HRMS *m*/*z* (ESI, positive) calcd for $C_{21}H_{27}NNaOSi^+$ $[M+Na]^+$: 360.1760, Found 360.1755.

4-methyl-4-phenylpyrrolidin-2-one (3p) [13)]



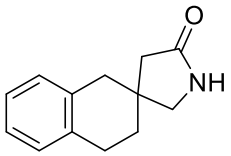
White solid (53.1 mg, 61%, 0.500 mmol scale, column eluent: ethyl acetate/methanol = 98/2); mp 123-125 ºC; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.38-7.34 (m, 2H), 7.28-7.20 (m, 3H), 5.90 (s, 1H), 3.68 (d, J = 9.6 Hz, 1H), 3.50 (dd, J = 8.8, 1.2 Hz, 1H), 2.79 (d, J = 16.4 Hz, 1H), 2.46 (d, J = 16.4 Hz, 1H), 1.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 177.6, 147.0, 128.8, 126.7, 125.4, 54.8, 44.4, 43.6, 29.9; HRMS *m*/*z* (ESI, positive) calcd for $C_{11}H_{14}NO^+$ $[M+H]^+$: 176.1075, Found 176.1069.

4-cyclopentylpyrrolidin-2-one (3q) [14)]



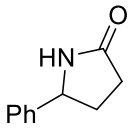
White solid (70.6 mg, 84%, 0.500 mmol scale, column eluent: ethyl acetate/methanol = 98/2); mp 130-132 ºC; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 5.73 (s, 1H), 3.15 (s, 2H), 2.18 (s, 2H), 1.57-1.40 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 178.2, 53.8, 43.2, 39.6, 36.9, 25.8, 23.0; HRMS *m*/*z* (ESI, positive) calcd for $C_9H_{16}NO^+$ $[M+H]^+$: 154.1232, Found 154.1225.

3,4-dihydro-1*H*-spiro[naphthalene-2,3'-pyrrolidin]-5'-one (3r)



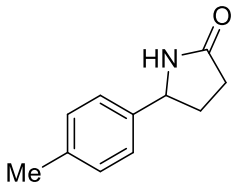
Yellowish solid (89.6 mg, 89%, 0.500 mmol scale, column eluent: ethyl acetate/methanol = 98/2); mp 146-150 ºC; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.37 (dd, J = 8.0, 1.2 Hz, 1H), 7.22-7.13 (m, 2H), 7.10-7.08 (m, 1H), 6.19 (s, 1H), 3.62 (d, J = 10.4 Hz, 1H), 3.44 (dd, J = 10.0, 0.8 Hz, 1H), 2.82 (t, J = 6.4 Hz, 2H), 2.76 (d, J = 17.6 Hz, 1H), 2.47 (d, J = 17.6 Hz, 1H), 2.02-1.97 (m, 1H), 1.92-1.78 (m, 3H),; ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 177.4, 141.8, 136.8, 129.5, 126.8, 126.6, 126.5, 57.2, 47.2, 42.1, 37.3, 30.2, 20.2; HRMS *m*/*z* (ESI, positive) calcd for $C_{13}H_{15}NNaO^+$ $[M+Na]^+$: 224.1051, Found 224.1046.

5-phenylpyrrolidin-2-one (5a) [13)]



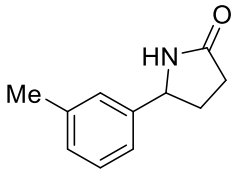
White solid (55.7 mg, 69%, 0.500 mmol scale, column eluent: ethyl acetate/methanol = 98/2); mp 99-103 ºC (107-108 ºC) [15)]; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.37 (t, J = 7.2 Hz, 2H), 7.28 (dd, J = 7.6 Hz, 3H), 6.43 (s, 1H), 4.75 (t, J = 7.2 Hz, 1H), 2.61-2.35 (m, 3H), 2.01-1.92 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 178.7, 142.6, 129.0, 128.0, 125.7, 58.2, 31.5, 30.4; HRMS *m*/*z* (ESI, positive) calcd for $C_{10}H_{12}NO^+$ $[M+H]^+$: 162.0919, Found 162.0913.

5-(*p*-tolyl)pyrrolidin-2-one (5b) [16)]



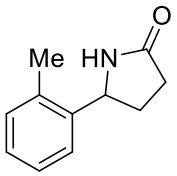
Yellow solid (61.8 mg, 71%, 0.500 mmol scale, column eluent: ethyl acetate/methanol = 98/2); mp 115-119 ºC (116-118 ºC) [17)]; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.18 (s, 4H), 5.93 (s, 1H), 4.72 (t, J = 6.8 Hz, 1H), 2.60-2.38 (m, 3H), 2.35 (s, 3H), 2.01-1.92 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 178.4, 139.6, 137.9, 129.7, 125.8, 58.0, 31.7, 30.5, 21.2; HRMS *m*/*z* (ESI, positive) calcd for $C_{11}H_{13}NNaO^+$ $[M+Na]^+$: 198.0895, Found 198.0889.

5-(*m*-tolyl)pyrrolidin-2-one (5c) [16)]



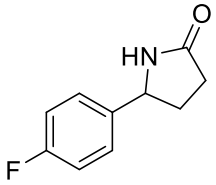
Yellow solid (76.7 mg, 88%, 0.500 mmol scale, column eluent: ethyl acetate/methanol = 98/2); mp 115-119 ºC; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.27-7.23 (m, 1H), 7.10 (t, J = 8.0 Hz, 3H), 6.28 (s, 1H), 4.71 (t, J = 7.2 Hz, 1H), 2.60-2.38 (m, 3H), 2.35 (s, 3H), 2.00-1.92 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 178.6, 142.6, 138.8, 128.9, 128.7, 126.4, 122.8, 58.1, 31.5, 30.4, 21.5; HRMS *m*/*z* (ESI, positive) calcd for $C_{11}H_{13}NNaO^+$ $[M+Na]^+$: 198.0895, Found 198.0890.

5-(*o*-tolyl)pyrrolidin-2-one (5d) [16]



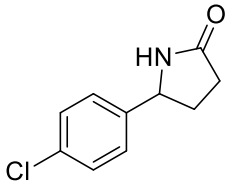
Yellowish solid (66.6 mg, 76%, 0.500 mmol scale, column eluent: ethyl acetate/methanol = 98/2); mp 123-125 ºC; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.34 (d, J = 7.6 Hz, 1H), 7.24-7.17 (m, 3H), 5.91 (s, 1H), 5.00 (t, J = 7.2 Hz, 1H), 2.68-2.59 (m, 1H), 2.51-2.38 (m, 2H), 2.35 (s, 3H), 1.93-1.84 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 178.6, 140.6, 134.6, 130.9, 127.7, 126.8, 124.1, 54.6, 29.9, 29.8, 19.1; HRMS *m*/*z* (ESI, positive) calcd for $C_{11}H_{13}NNaO^+$ $[M+Na]^+$: 198.0895, Found 198.0890.

5-(4-fluorophenyl)pyrrolidin-2-one (5e) [16]



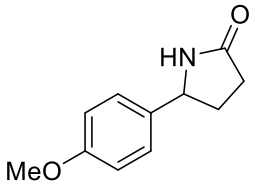
White solid (64.7 mg, 72%, 0.500 mmol scale, column eluent: ethyl acetate/methanol = 98/2); mp 128-130 ºC (138-139 ºC) [15]; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.29-7.25 (m, 2H), 7.09-7.03 (m, 2H), 6.20 (s, 1H), 4.75 (t, J = 7.2 Hz, 1H), 2.61-2.52 (m, 1H), 2.51-2.34 (m, 2H), 2.02-1.90 (m, 1H); ^{19}F NMR (376 MHz, $CDCl_3$, ppm) δ -117.4; ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 178.5, 162.5 (q, J = 245 Hz), 138.3, (q, J = 3 Hz), 127.5 (q, J = 8 Hz), 116.0 (q, J = 22 Hz), 57.6, 31.7, 30.4; HRMS *m*/*z* (ESI, positive) calcd for $C_{10}H_{10}FNNaO^+$ $[M+Na]^+$: 202.0644, Found 202.0639.

5-(4-chlorophenyl)pyrrolidin-2-one (5f) [16]



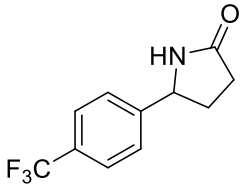
Yellowish solid (75.1 mg, 77%, 0.500 mmol scale, column eluent: ethyl acetate/methanol = 98/2); mp 95-98 ºC; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.35 (dd, J = 8.8, 2.0 Hz, 2H), 7.24 (dd, J = 8.8, 2.0 Hz, 2H), 6.33 (s, 1H), 4.74 (t, J = 7.2 Hz, 1H), 2.62-2.53 (m, 1H), 2.52-2.35 (m, 2H), 1.98-1.88 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 178.6, 141.1, 133.8, 129.2, 127.2, 57.6, 31.5, 30.3; HRMS *m*/*z* (ESI, positive) calcd for $C_{10}H_{11}ClNO^+$ $[M+H]^+$: 196.0529, Found 196.0524.

5-(4-methoxyphenyl)pyrrolidin-2-one (5g) [16]



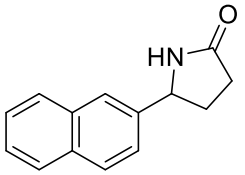
White solid (75.2 mg, 79%, 0.500 mmol scale, column eluent: ethyl acetate/methanol = 98/2); mp 126-129 ºC (115-116 ºC) [15]; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.22 (d, J = 8.4 Hz, 2H), 6.90 (d, J = 8.0 Hz, 2H), 5.98 (s, 1H), 4.71 (t, J = 7.2 Hz, 1H), 3.81 (s, 3H), 2.58-2.36 (m, 3H), 2.00-1.91 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 178.4, 159.5, 124.5, 127.1, 114.4, 57.8, 55.5, 31.8, 30.5; HRMS m/z (ESI, positive) calcd for $C_{11}H_{13}NNaO_2^+$ $[M+Na]^+$: 214.0844, Found 214.0838.

5-(4-(trifluoromethyl)phenyl)pyrrolidin-2-one (5h) [18]



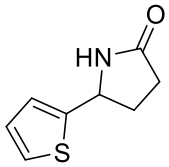
White solid (94.2 mg, 82%, 0.500 mmol scale, column eluent: ethyl acetate/methanol = 98/2); mp 88-92 ºC; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.64 (d, J = 12.4 Hz, 2H), 7.43 (d, J = 8.0 Hz, 2H), 6.08 (s, 1H), 4.83 (t, J = 7.2 Hz, 1H), 2.68-2.59 (m, 1H), 2.54-2.40 (m, 2H), 2.01-1.92 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 179.0, 146.7, 130.3 (q, J = 32 Hz), 126.1, 125.8 (q, J = 4 Hz), 124.1 (q, J = 272 Hz), 57.8, 31.2, 30.3; ^{19}F NMR (376 MHz, $CDCl_3$, ppm) δ -65.8; HRMS m/z (ESI, positive) calcd for $C_{11}H_{11}F_3NO^+$ $[M+H]^+$: 230.0793, Found 230.0782.

5-(naphthalen-2-yl)pyrrolidin-2-one (5i) [16]



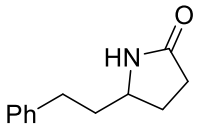
Yellow solid (47.5 mg, 45%, 0.500 mmol scale, column eluent: ethyl acetate/methanol = 98/2); mp 167-170 ºC; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.88-7.81 (m, 3H), 7.74 (s, 1H), 7.53-7.47 (m, 2H), 7.41 (dd, J = 8.8, 2.0 Hz, 1H), 5.92 (s, 1H), 4.92 (t, J = 7.2 Hz, 1H), 2.70-2.61 (m, 1H), 2.58-2.42 (m, 2H), 2.12-2.03 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 178.5, 139.9, 133.4, 133.2, 129.2, 128.0, 127.9, 126.7, 126.4, 124.5, 123.7, 58.2, 31.4, 30.3; HRMS m/z (ESI, positive) calcd for $C_{14}H_{14}NO^+$ $[M+H]^+$: 212.1075, Found 212.1068.

5-(thiophen-2-yl)pyrrolidin-2-one (5j) [19]



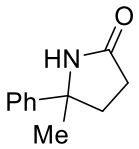
Brownish solid (73.5 mg, 88%, 0.500 mmol scale using 5 mol% TsOH, column eluent: ethyl acetate/methanol = 98/2); mp 113-116 ºC (115 ºC) [20]; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.26-7.25 (m, 1H), 6.99-6.96 (m, 2H), 6.16 (s, 1H), 5.03 (t, J = 6.8 Hz, 1H), 2.66-2.37 (m, 3H), 2.18-2.10 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 177.7, 146.6, 127.1, 125.1, 124.3, 54.0, 31.9, 30.2; HRMS *m/z* (ESI, positive) calcd for $C_8H_9NNaOS^+$ $[M+Na]^+$: 190.0303, Found 190.0298.

5-phenethyl-pyrrolidin-2-one (5k) [22]



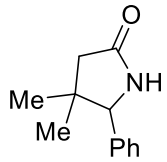
White solid (72.3 mg, 76%, 0.500 mmol scale, column eluent: ethyl acetate/methanol = 98/2); mp 72-74 ºC; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.30 (t, J = 7.2 Hz, 2H), 7.23-7.17 (m, 3H), 5.88 (s, 1H), 3.65 (quint, J = 6.4 Hz, 1H), 2.67 (t, J = 8.0 Hz, 2H), 2.40-2.24 (m, 3H), 1.92-1.72 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 178.7, 141.2, 128.6. 128.4, 126.2, 54.2, 38.6, 32.4, 30.4, 27.3; HRMS *m/z* (ESI, positive) calcd for $C_{12}H_{16}NO^+$ $[M+H]^+$:190.1226, Found 190.1224.

5-methyl-5-phenylpyrrolidin-2-one (5l) [19]



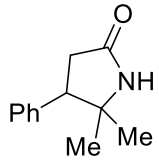
White solid (55.4 mg, 63%, 0.500 mmol scale, column eluent: ethyl acetate/methanol = 98/2); mp 77-79 ºC (117 ºC) [23]; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.36 (s, 2H), 7.32-7.26 (m, 2H), 6.18 (s, 1H), 2.42 (quint, J = 7.6 Hz, 2H), 2.29 (t, J = 8.0 Hz, 2H), 1.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 177.6, 146.5, 128.8, 127.3, 124.6, 61.9, 38.0, 30.4, 29.5; HRMS *m/z* (ESI, positive) calcd for $C_{11}H_{13}NNaO^+$ $[M+Na]^+$: 198.0895, Found 198.0890.

4,4-dimethyl-5-phenylpyrrolidin-2-one (7a)



White solid (82.6 mg, 87%, 0.500 mmol scale, column eluent: ethyl acetate/methanol = 98/2); mp 143-146 ºC; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.39-7.30 (m, 3H), 7.23 (d, J = 6.8 Hz, 2H), 5.95 (s, 1H), 4.44 (s, 1H), 2.29 (s, 2H), 1.28 (s, 3H), 0.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 177.5, 138.2, 128.6, 128.2, 126.7, 68.2, 45.6, 40.5, 28.1, 24.4; HRMS m/z (ESI, positive) calcd for $C_{12}H_{15}NNaO^+$ $[M+Na]^+$: 212.1051, Found 212.1045.

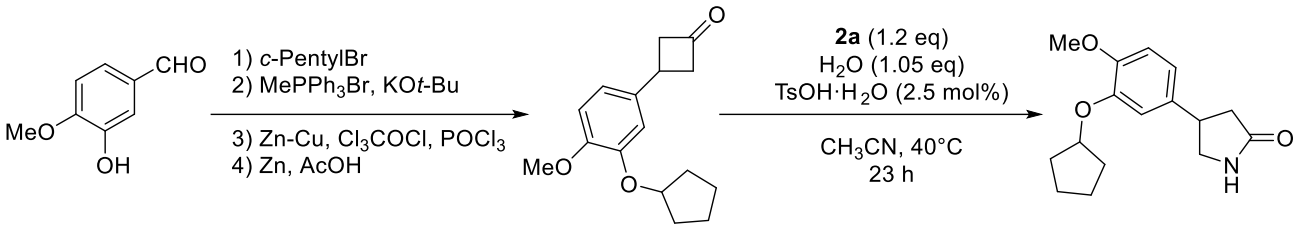
5, 5-dimethyl-4-phenylpyrrolidin-2-one (7b) [24)]



White solid (48.2 mg, 51%, 0.500 mmol scale, column eluent: ethyl acetate/methanol = 98/2); mp 122-128 ºC (129-131ºC) [25)]; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.37-7.28 (m, 3H), 7.24 (d, J = 7.2 Hz, 2H), 5.89 (s, 1H), 3.41 (dd, J = 10.0, 8.8 Hz, 1H), 2.84 (dd, J = 16.8, 10.0 Hz, 1H), 2.67 (dd, J = 16.8, 8.4 Hz, 1H), 1.39 (s, 3H), 0.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 175.8, 138.1, 128.6, 128.4, 127.6, 59.9, 51.8, 36.0, 29.0, 25.0; HRMS m/z (ESI, positive) calcd for $C_{12}H_{15}NNaO^+$ $[M+Na]^+$: 212.1051, Found 212.1045.

3. Synthetic Applications

3. 1. Synthesis of Rolipram [26-28)]



Step 1: To a 500 ml three-necked flask was added K_2CO_3 (112 mmol, 2.0 eq), bromocyclopentane (112 mmol, 2.0 eq)), isovanillin (55.9 mmol, 1.0 eq), DMF (0.33 M) at room temperature under N_2. Then the reaction mixtures were warmed to 100 ˚C and stirred for 2 hours. The reaction was quenched by water at room temperature and worked up with AcOEt (100 mL× 3). The combined organic layer was washed with water and brine and dried over Na_2SO_4. After removal of Na_2SO_4 by filtration, the collected solution was evaporated under reduced pressure and the remained crude mixture was purified by silica gel column chromatography (hexane/ ethyl acetate = 80/20).

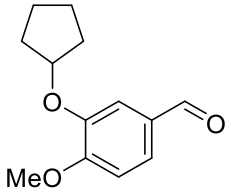
Step 2: To a 500 ml three-necked flask was added Wittiz reagent (59.0 mmol, 1.3 eq), THF (0.50 M) at room temperature under argon atmosphere. The reaction mixtures were cooling to 0 ˚C and dropwised KO*t*-Bu (59.0 mmol, 1.3 eq) in THF (1.0 M for KO*t*-Bu). After addition, the reaction was warmed to room temperature and stirred for 10 minutes. After 10 minutes, the reaction mixtures were cooling to 0 ˚C again and dropwised 3-(cyclopentyloxy)-4-methoxybenzaldehyde (45.4 mmol, 1.0 eq) in THF (2.0 M). Then the reaction was stirred at room temperature for 12 hours. After starting material was disappeared on the TLC, the mixture solution was filtered through a pad of celite and washed with Et_2O (30 ml × 3). The combined solution was evaporated under reduced pressure and the remained crude mixture was purified by silica gel column chromatography (hexane/ ethyl acetate = 90/10).

Step 3: To a 500 ml three-necked flask was added Zn-Cu (82.5 mmol, 3.0 eq), olefin (27.5 mmol, 1.0 eq), Et_2O (0.5 M) at room temperature under argon atmosphere. To the reaction mixtures was dropwised 2,2,2-trichloroacetyl chloride (55.0 mmol, 2.0 eq), $POCl_3$ (30.2 mmol, 1.1 eq) in Et_2O solution (2.0 M) using dropping funnel at 40 ˚C and stirred overnight at reflux. After starting material was disappeared on the TLC, the mixture solution was filtered through a pad of celite and washed with Et_2O (30 ml × 3). The combined organic phase was washed with sat. $NaHCO_3$ aq. and brine and dried over $MgSO_4$. After removal of $MgSO_4$ by filtration, the collected solution was evaporated under reduced pressure and the remained crude mixture was used to next reaction.

Step 4: To a 500 ml flask was added Zn dust (69.3 mmol, 4.0 eq), AcOH (2.0 M) at room temperature under argon atmosphere. The crude obtained in previous reaction was dissolved in AcOH solution (1.0 M) and dropwised to the reaction mixtures at 0 ˚C. Then, the reaction mixtures was stirred for 2 h at 70 ˚C. After starting material was disappeared on the TLC, the mixture solution filtered through a pad of celite and washed with Et_2O (30 ml × 3). The combined organic phase was washed with sat. $NaHCO_3$ aq. and brine and dried over $MgSO_4$. After removal of $MgSO_4$ by filtration, the collected solution was evaporated under reduced pressure and the remained crude mixture was purified by silica gel column chromatography (toluene/ ethyl acetate = 95/5).

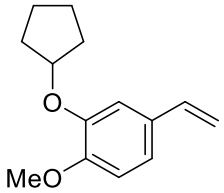
Step 5: The method was same as general procedure for synthesis of γ-lactam from cyclobutanones.

3-(cyclopentyloxy)-4-methoxybenzaldehyde [29]



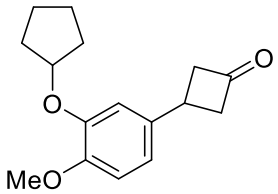
Yellow liquid (11.4 g, 93%, 55.9 mmol scale, column eluent: hexane/ethyl acetate = 8/2); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.84 (s, 1H), 7.42 (td, J = 8.0, 2.0 Hz, 2H), 6.97 (d, J = 8.4 Hz, 1H), 4.86 (sep, J = 3.2 Hz, 1H), 3.93 (s, 3H), 2.04-1.95 (m, 2H), 1.91-1.79 (m, 4H), 1.68-1.59 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 191.1, 155.4, 148.3, 130.0, 126.4, 112.0, 110.8, 80.4, 56.2, 32.8, 24.1; HRMS m/z (ESI, positive) calcd for $C_{13}H_{17}O_3^+$ $[M+H]^+$: 221.1172, Found 221.1170.

2-(cyclopentyloxy)-1-methoxy-4-vinylbenzene [29]



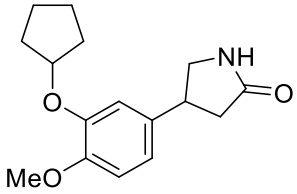
Yellow liquid (7.29 g, 74%, 45.4 mmol scale, column eluent: hexane/ethyl acetate = 9/1); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 6.97 (d, J = 2.4 Hz, 1H), 6.93 (dd, J = 8.4, 2.0 Hz, 1H), 6.81 (d, J = 8.0 Hz, 1H), 6.64 (dd, J = 17.6, 10.8 Hz, 1H), 5.61-5.57 (m, 1H), 5.14-5.11 (m, 1H), 4.82-4.79 (m, 1H), 3.84 (s, 3H), 2.00-1.79 (m, 6H), 1.66-1.56 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 150.1, 147.8, 136.7, 130.7, 119.4, 112.5, 111.8, 111.8, 80.5, 56.2, 33.0, 24.2; HRMS m/z (ESI, positive) calcd for $C_{14}H_{19}O_2^+$ $[M+H]^+$: 219.1380, Found 219.1378.

3-(3-(cyclopentyloxy)-4-methoxyphenyl)cyclobutan-1-one (9) [29]



Yellow liquid (746 mg, 10%, 27.5 mmol scale, column eluent: toluene/ethyl acetate = 95/5); ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 6.86-6.80 (m, 3H), 4.81-4.76 (s, 1H), 3.84 (s, 3H), 3.62 (quin, J = 8.8 Hz, 1H), 3.52-3.43 (m, 2H), 3.25-3.17 (m, 2H), 1.98-1.79 (m, 6H), 1.68-1.57 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 207.3, 148.9, 147.9, 136.2, 118.5, 113.8, 112.1, 80.6, 56.2, 54.9, 32.9, 28.2, 24.1; HRMS m/z (ESI, positive) calcd for $C_{16}H_{21}O_3^+$ $[M+H]^+$: 261.1485, Found 261.1483.

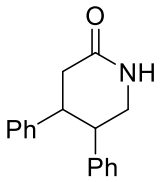
Rolipram (10) [29]



White solid (86.3 mg, 63%, 0.500 mmol scale, column eluent: ethyl acetate/methanol = 98/2); mp 132-133 ºC (132-133ºC) [30]; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 6.84-6.76 (m, 3H), 5.70 (br, 1H), 4.79-4.75 (m, 1H), 3.84 (s,3H), 3.75 (t, J = 9.2 Hz, 1H), 3.63 (q, J = 8.8 Hz, 1H), 3.38 (dd, J = 7.6, 7.2 Hz, 1H), 2.71 (dd J = 8.8, 8.8 Hz,1H), 2.47 (dd, J = 9.2, 8.8 Hz, 1H), 1.95-1.91 (m, 6H), 1.65-1.60 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 178.2, 149.2, 147.9, 134.7, 118.9, 113.9, 112.3, 80.6, 56.2, 49.9, 40.0, 38.4, 32.9, 24.1; HRMS *m*/*z* (ESI, positive) calcd for $C_{16}H_{22}NO_3^+$ $[M+H]^+$: 276.1594, Found 276.1591.

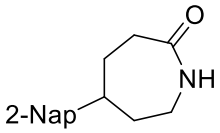
3. 2. Lactam synthesis from other substituted cyclic ketones

***cis*-4,5-Diphenyl-2-piperidinone (12a)**



Procedure was same as synthesis of γ-lactam from cyclobutanones; White solid (48.2 mg, 39%, 0.500 mmol scale, column eluent: ethyl acetate/methanol = 98/2); mp 191-198 ºC; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.21-7.16 (m, 6H), 6.79-6.76 (m, 4H), 6.13 (s, 1H), 3.66-3.63 (m, 2H), 3.53-3.46 (m, 2H), 2.85 (dd, J = 6.0, 6.0 Hz, 1H), 2.73 (dd, J = 6.0, 6.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 172.6, 139.7, 139.2, 128.5, 128.3, 128.1, 127.1, 127.0, 43.9, 43.4, 43.4, 43.3, 35.4; HRMS *m*/*z* (ESI, positive) calcd for $C_{17}H_{18}NO^+$ $[M+H]^+$: 252.1383, Found 252.1378.

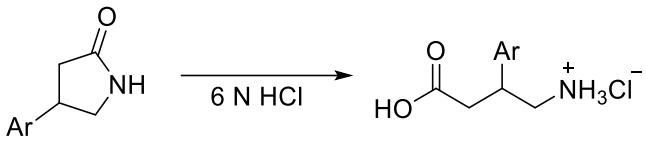
5-(2-naphthyl)-azepan-2-one (12b)



Procedure was same as synthesis of γ-lactam from cyclobutanones; White solid (73.7 mg, 66%, 0.500 mmol scale, column eluent: ethyl acetate/methanol = 98/2); mp 209-212 ºC; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.82-7.78 (m, 3H), 7.62 (s, 1H), 7.49-7.42 (m, 2H), 7.32 (dd, J = 8.4, 1.6 Hz, 1H), 5.93 (s, 1H), 3.50-3.43 (m, 1H), 3.38-3.30 (m, 1H), 2.95 (tt, J = 12, 3.2 Hz, 1H), 2.72-2.60 (m, 2H), 2.13-2.08 (m, 2H), 1.97-1.80 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 178.6, 143.9, 133.7, 132.4, 128.4, 127.8, 127.7, 126.2, 125.6, 124.9, 49.0, 42.2, 37.5, 36.0, 30.6; HRMS *m*/*z* (ESI, positive) calcd for $C_{16}H_{18}NO^+$ $[M+H]^+$: 240.1383, Found 240.1380.

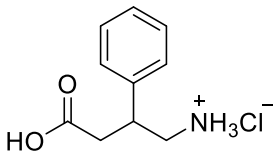
3. 3. Synthesis of γ-aminobutyric acids derivatives from γ-lactam

Procedure for ring-opening reaction for synthesis of γ-aminobutyric acids derivatives [31)]



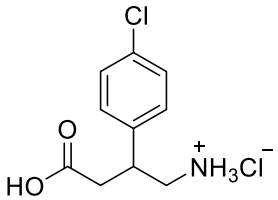
To a test tube was added to γ-lacatam (1.0 eq), 6 N HCl (0.075 M), then the solution was refluxed at 120 ˚C for 24 hours. After cooling the reaction mixtures to room temperature, the solvent was removed under reduced pressure and isolated yield.

3-Carboxy-2-phenylpropan-1-ammonium chloride (13a) [32)]



White solid (129 mg, 92%, 0.65 mmol scale); mp 169-172 ºC; ^{1}H NMR (400 MHz, D_2O, ppm) δ 7.34-7.31 (m, 2H), 7.27-7.25 (m, 3H), 3.35-3.25 (m, 2H), 3.13 (dd, J = 12.0, 11.2 Hz, 1H), 2.75 (dd, J = 16.0, 6.0 Hz, 1H), 2.64 (dd, J = 16.0, 8.8 Hz, 1H); ^{13}C NMR (100 MHz, D_2O, ppm) δ 175.5, 138.4, 129.4, 128.4, 127.9, 43.9, 40.0, 38.3; HRMS *m*/*z* (ESI, positive) calcd. for $C_{10}H_{14}NO_2^+$ $[M+H]^+$: 180.1019, Found 180.1018.

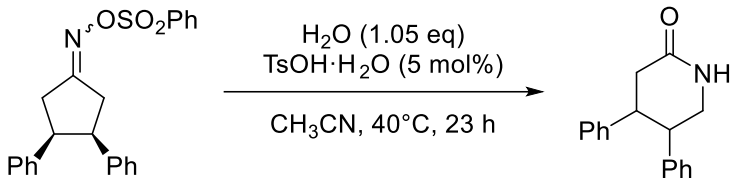
3-Carboxy-2-(4-chlorophenyl)propan-1- ammonium chloride (13b) [33)]



White solid (48.9 mg, 89%, 0.22 mmol scale); mp 161-168 ºC; ^{1}H NMR (400 MHz, D_2O, ppm) δ 7.42 (d, J = 8.8 Hz, 2H), 7.32 (d, J = 8.8 Hz, 2H), 3.43-3.34 (m, 2H), 3.24-3.19 (m, 1H), 2.83 (dd, J = 16.1, 7.6 Hz, 1H), 2.72 (dd, J = 16.1, 7.6 Hz, 1H); ^{13}C NMR (100 MHz, D_2O, ppm) δ 175.4, 137.0, 133.4, 129.5, 129.3, 43.6, 39.5, 38.3; HRMS *m*/*z* (ESI, positive) calcd. for $C_{10}H_{13}ClNO_2^+$ $[M+H]^+$: 214.0629, Found 214.0628.

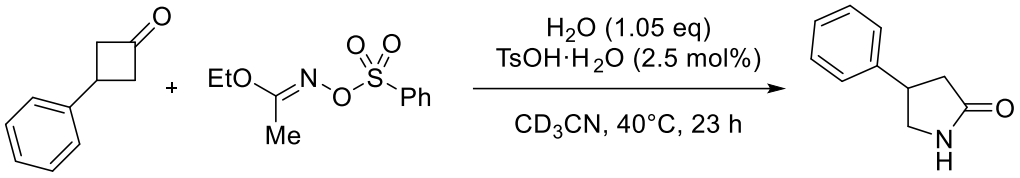
4. Mechanistic study

4.1. Reaction with ketoxime intermediate under standard conditions



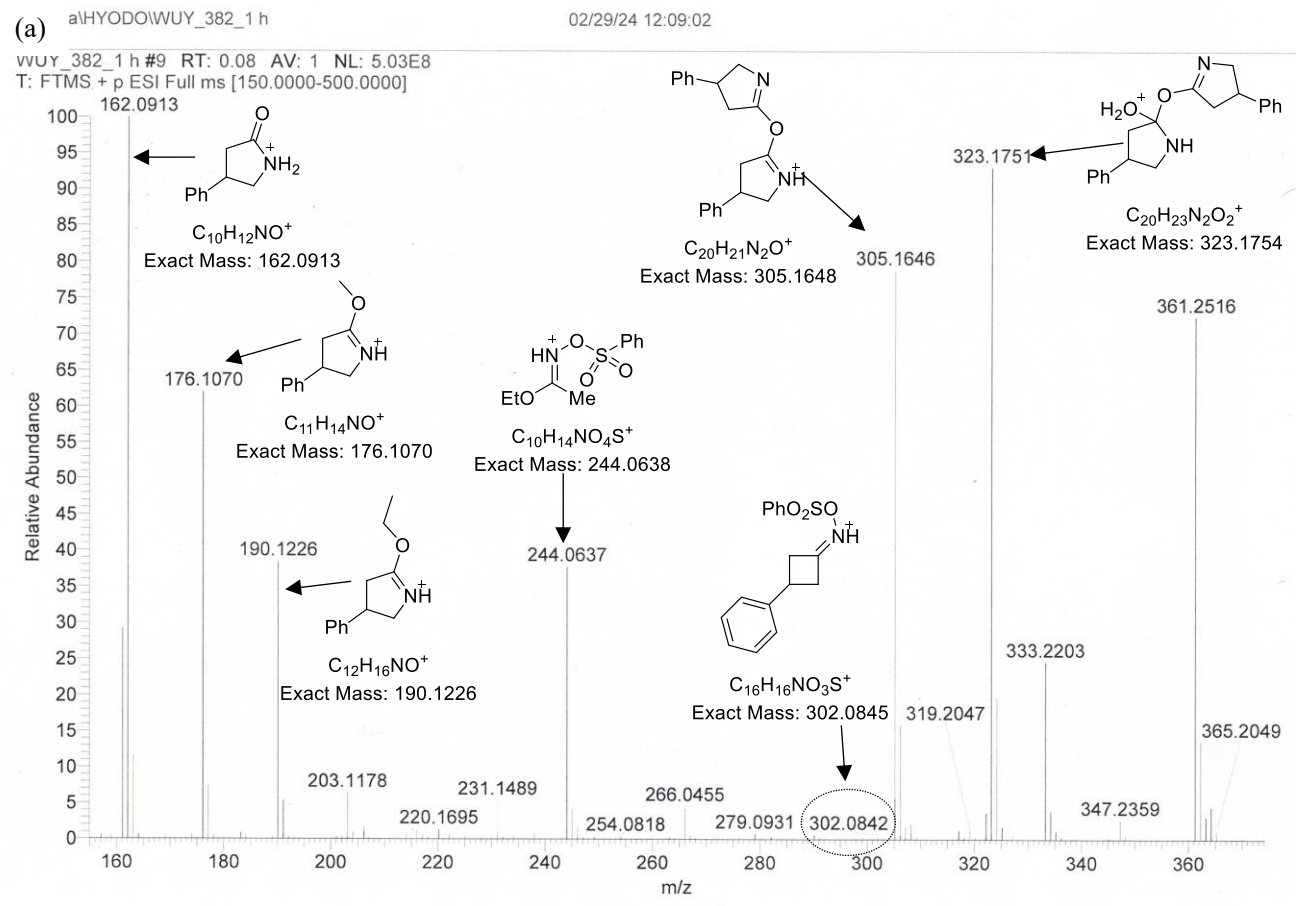
To a test tube was added cyclopentanone oxime **14** (0.250 mmol, 1.0 eq)[1], H_2O (1.05 eq), $TsOH·H_2O$ (5 mol%), CH_3CN (1.0 M) under N_2 at indicated temperature. After 23 hours, the crude mixture was quenched by sat. $NaHCO_3$ (3 mL) and work up with ethyl acetate (10 ml × 3). The combined organic phase was washed with brine and dried over Na_2SO_4. After removal of Na_2SO_4 by filtration, the collected solution was evaporated under reduced pressure and the remained crude mixture was purified by silica gel column chromatography (ethyl acetate/methanol = 98/2) The product **12a** was isolated (10.6 mg, 17%).

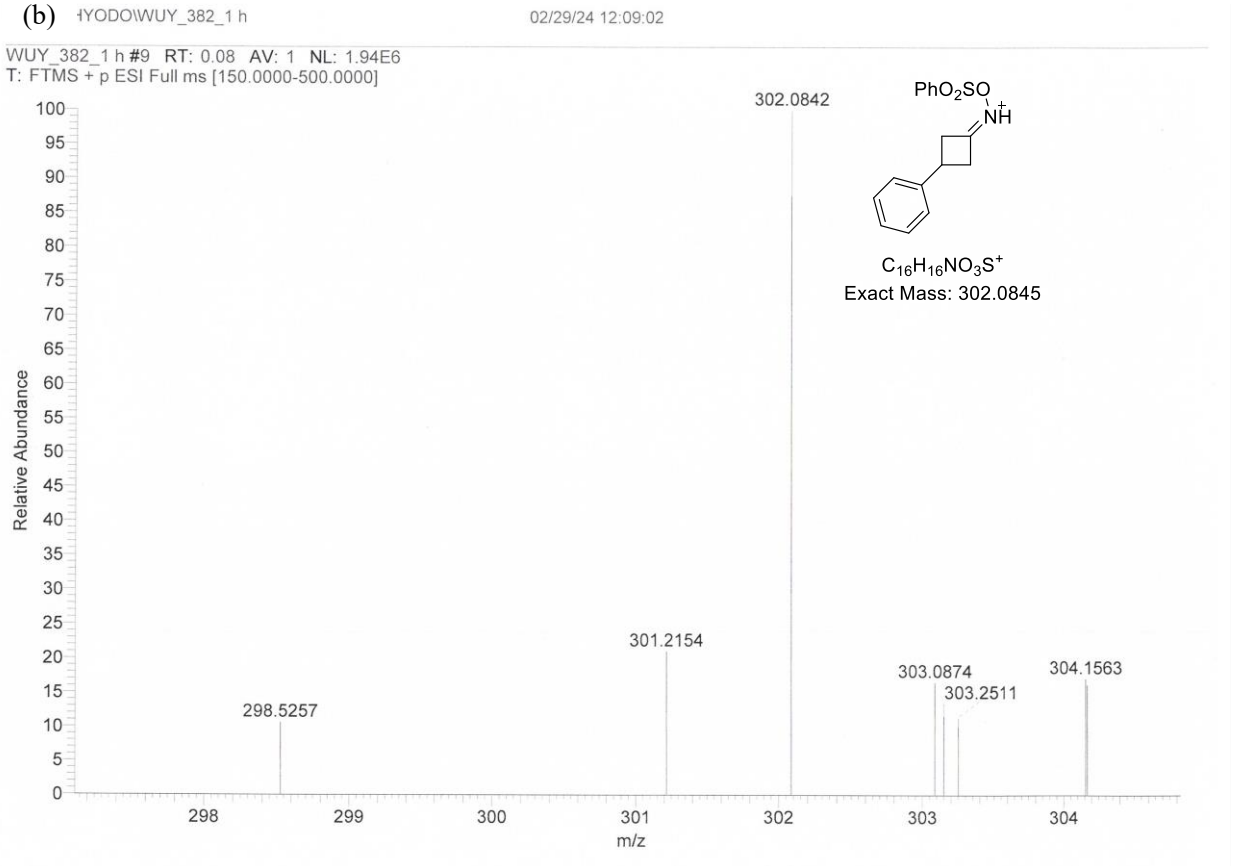
4.2. Observation of reaction behavior in-situ monitored by HRMS



To a test tube was added cyclobutanone (0.500 mmol, 1.0 eq), oxime (0.600 mmol, 1.2eq), $TsOH·H_2O$ (0.0125 mmol, 2.5 mol%), acetonitrile (1.0 M) under N_2 at 40°C. At 1 hours after the reaction started, a part (9.5 μL) of reaction mixtures was taken by micropipette and transferred to vial, then which was diluted to MeOH (1 mL) solution for sample preparation of ESI-MS (Thermo Scientific Exactive Plus) measurement (Figure S1(a), (b)). The sample was measured by another ESI-MS (JEOL AccuTOF LC- plus 4G system with 1260 Infinity HPLC) (Figure S1(c)).

From the MS spectra, a trace amount of ketoxime ester was observed. HRMS *m/z* (ESI, positive) calcd. for $C_{16}H_{16}NO_3S^+$ $[M+H]^+$: 302.0845, Found: 302.0842. Interestingly, we assumed that adduct of lactam to cyclic carbocation was appeared at 305.1646; HRMS *m/z* (ESI, positive) calcd. for $C_{20}H_{21}N_2O^+$ $[M+H]^+$: 305.1648, Found: 305.1646. Moreover, adduct attached water was also generated at 323.1751; HRMS *m/z* (ESI, positive) calcd. for $C_{20}H_{23}N_2O_2^+$ $[M+H]^+$: 323.1754, Found: 323.1751. Based on these results, the reaction proceeded *via* ketoxime ester and cyclic carbocation (nitrilium ion). Therefore, the reaction mechanism indicated that the reaction occurred through Beckmann rearrangement.


(a)
a\HYODO\WUY_382_1 h
02/29/24 12:09:02
WUY_382_1 h #9 RT: 0.08 AV: 1 NL: 5.03E8
T: FTMS + p ESI Full ms [150.0000-500.0000]
Relative Abundance
m/z
162.0913
C10H12NO+
Exact Mass: 162.0913
176.1070
C11H14NO+
Exact Mass: 176.1070
190.1226
C12H16NO+
Exact Mass: 190.1226
244.0637
C10H14NO4S+
Exact Mass: 244.0638
305.1646
C20H21N2O+
Exact Mass: 305.1648
323.1751
C20H23N2O2+
Exact Mass: 323.1754
361.2516
333.2203
319.2047
365.2049
347.2359
302.0842
C16H16NO3S+
Exact Mass: 302.0845
279.0931
266.0455
254.0818
231.1489
220.1695
203.1178


(b)
HYODO\WUY_382_1 h
02/29/24 12:09:02
WUY_382_1 h #9 RT: 0.08 AV: 1 NL: 1.94E6
T: FTMS + p ESI Full ms [150.0000-500.0000]
Relative Abundance
m/z
302.0842
C16H16NO3S+
Exact Mass: 302.0845
301.2154
303.0874
303.2511
304.1563
298.5257

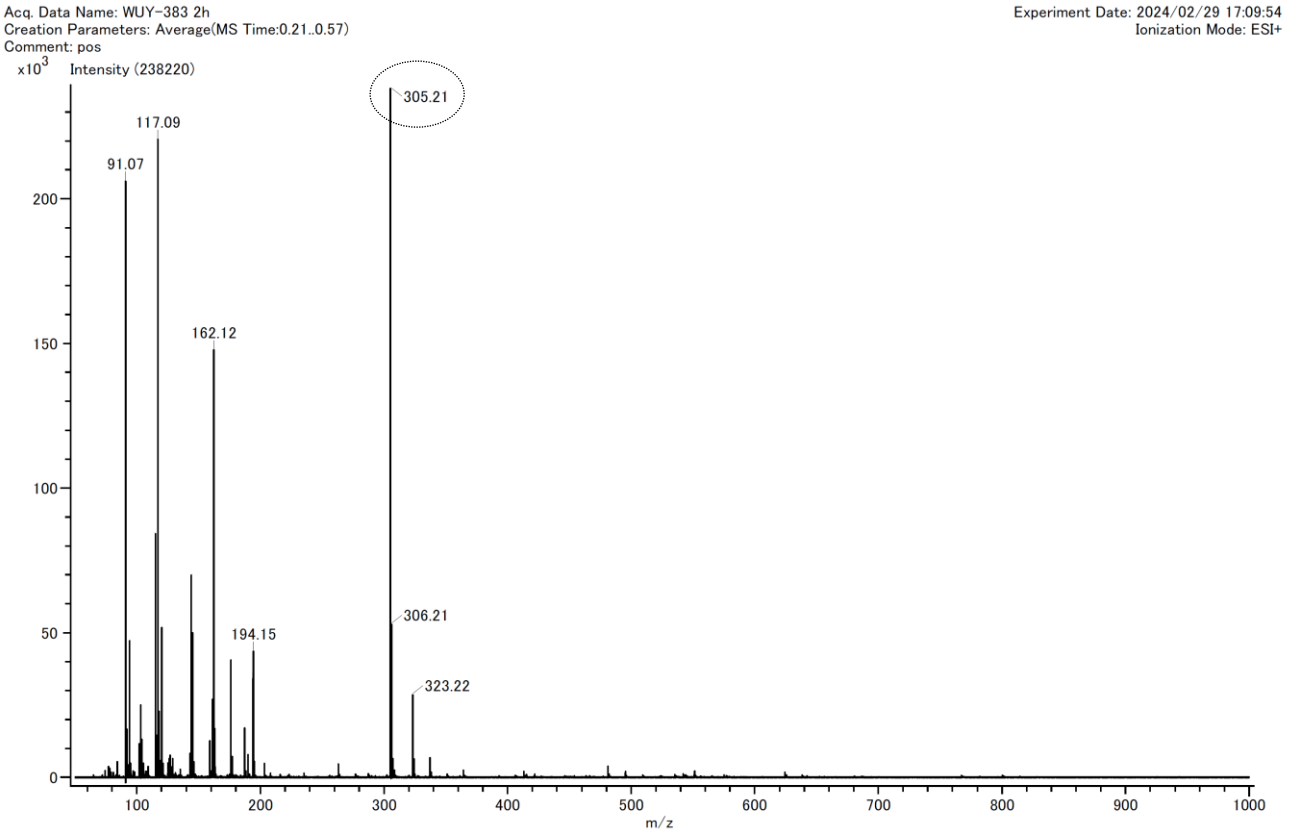
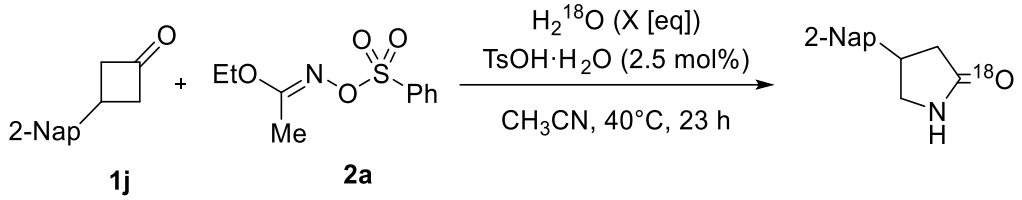


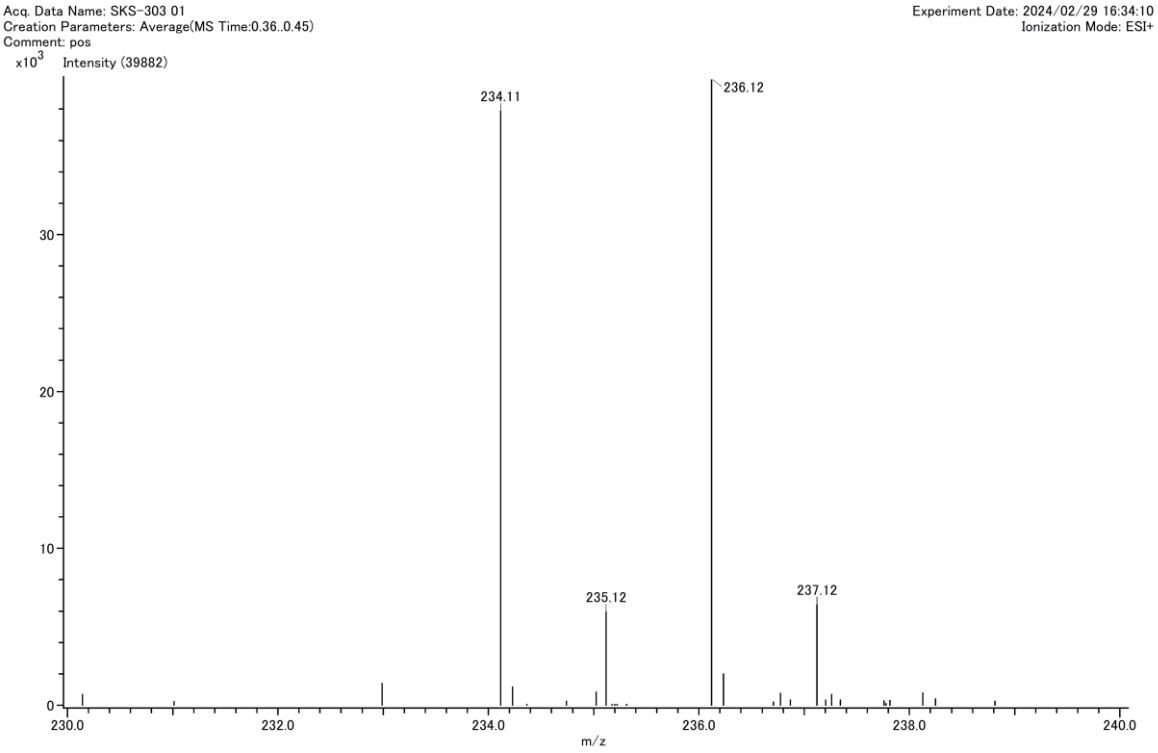
Figure S1. ESI-MS spectra for observation of reaction *in-situ*. (a) Overall view. (b) Enlarged view. (c) Overall view by anther ESI-low MS.

4.3. Isotope experiment using 18O-water under standard condition



To a test tube was added cyclobutanone **1j** (0.500 mmol, 1.0 eq), oxime (0.600 mmol, 1.2eq), TsOH·H_2O (0.0125 mmol, 2.5 mol%), H_2O (0.525x [mmol], x [eq], x = 1.05, 2.1), acetonitrile (1.0 M) under N_2 at 40°C. After indicated time, the reaction mixture was quenched by sat. $NaHCO_3$ (3 mL) and work up with ethyl acetate (10 ml × 3). The combined organic phase was washed with brine and dried over Na_2SO_4. After removal of Na_2SO_4 by filtration, the collected solution was evaporated under reduced pressure and the remained crude mixture was purified by silica gel column chromatography (ethyl acetate/methanol = 98/2). The product **3j** was isolated (x = 1.05: 76.6 mg, 73%; x = 2.1: 68.2 mg, 65%) and measured by ESI-MS. The ration of 18O-product was calculated from the result of ESI-MS (Figure S2, S3).[34)]

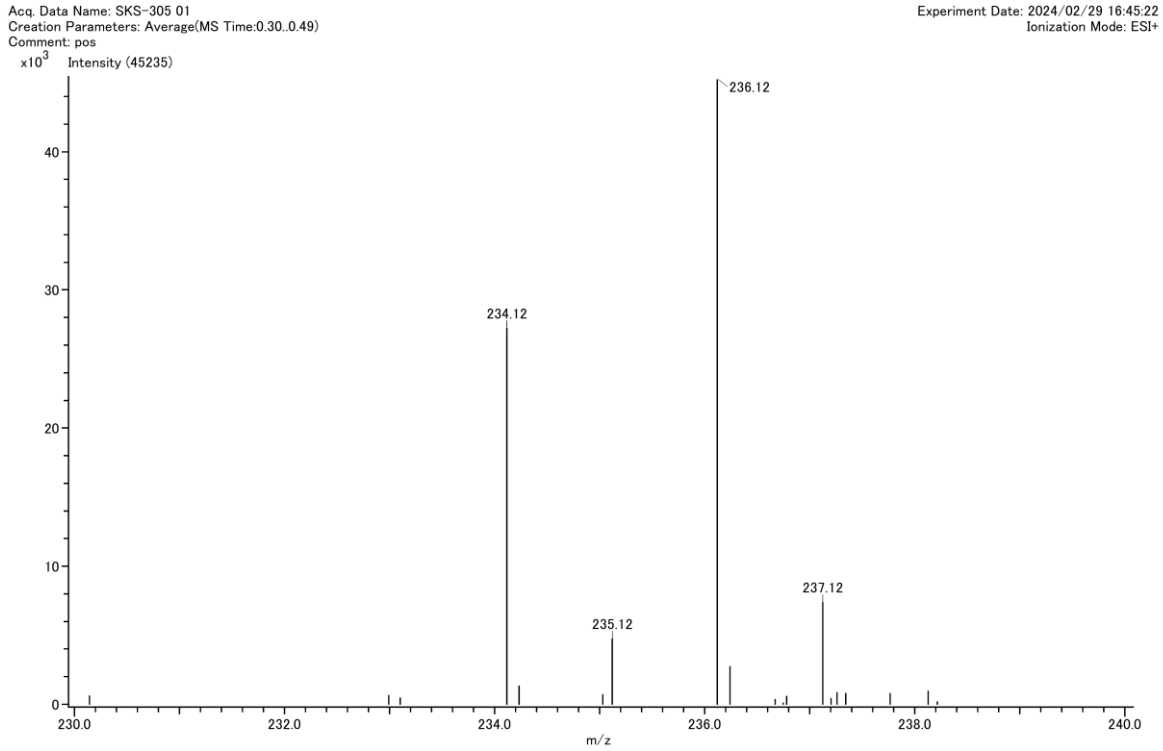
Detection of 18O ratio of product after isotope experiments by ESI-MS



m/z	Intensity	Abundance
234.11	**37831**	**94.9**
235.12	5922	14.8
236.12	**39882**	**100.0**
237.12	6371	16.0

Figure S2. ESI spectra of 18O enriched **3j** used 18O-water (1.05 eq)

18O atm% of **3j**: (100-94.9*0.20%)/(100-94.9*0.20%+94.9) = 51.3%



m/z	Intensity	Abundance
234.12	**27182**	**60.1**
235.12	4704	10.4
236.12	**45235**	**100.0**
237.12	7329	16.2

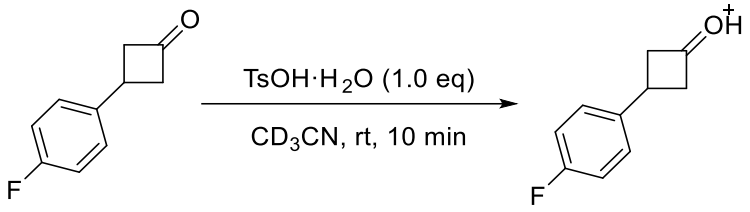
Figure S3. ESI spectra of 18O enriched **3j** used 18O-water (2.1 eq)

18O atm% of **3j**: (100-60.1*0.20%)/(100-60.1*0.20%+60.1) = 62.4%

4.5. Observation of reaction behavior using cyclobutanone *in-situ* monitored by ^{19}F NMR

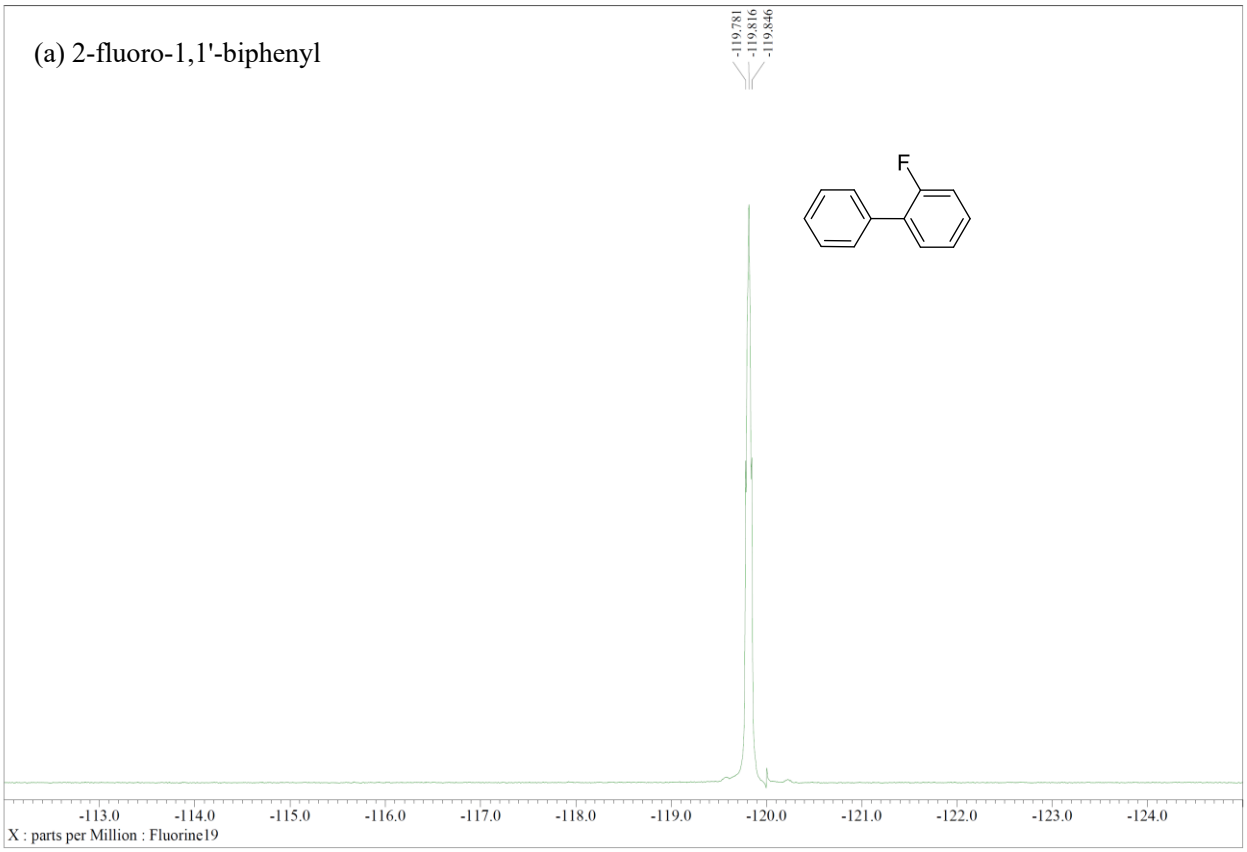
First, we prepared ^{19}F NMR for each reagent and ^{19}F NMR for each reagent with acid because the chemical shift was possible to change in the presence of acid (Figure S4, S5). The obtained ^{19}F NMR data were utilized to identify each compound on the ^{19}F NMR of reaction behavior in-situ (Figure S6).

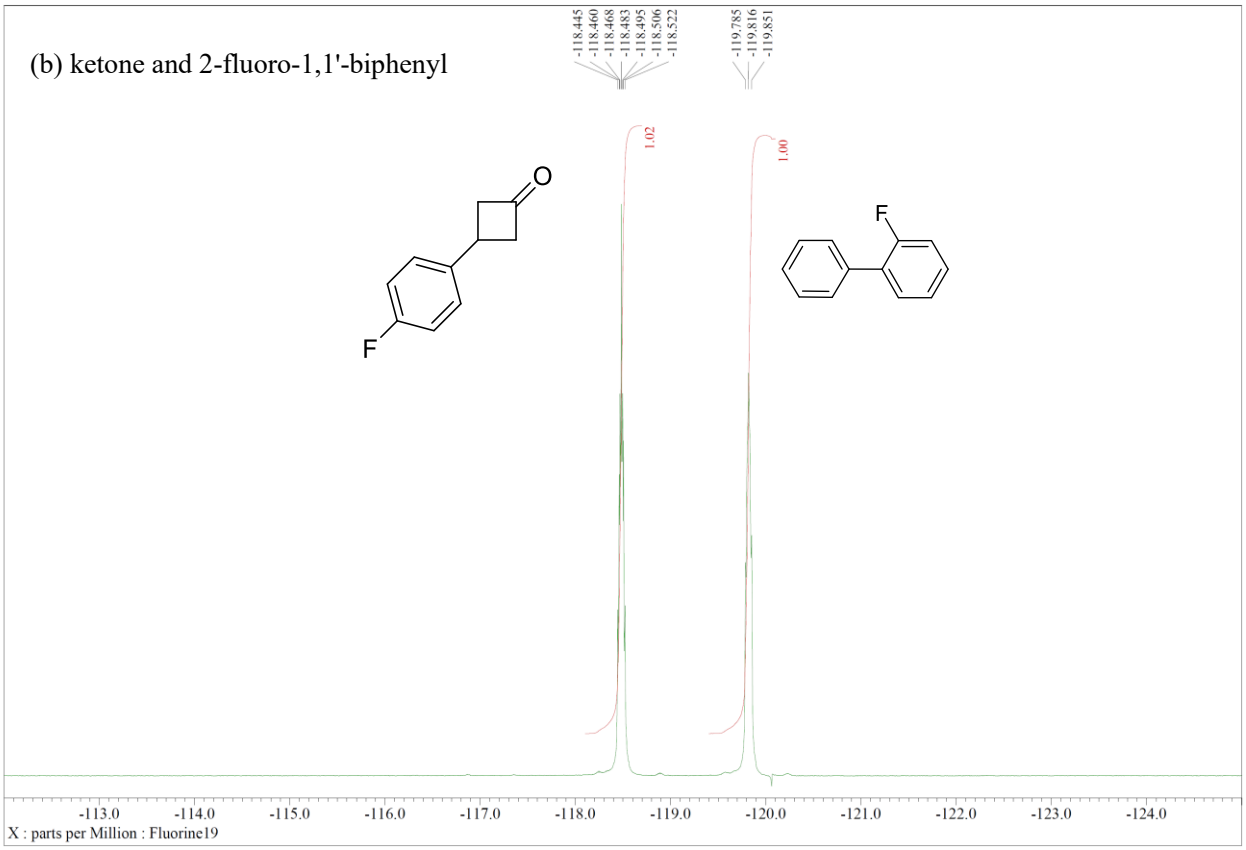
Ketone and acids



To NMR tube was added to ketone (10 mg, 0.0609 mmol, 1.0 eq.), 2-fluoro-1,1'-biphenyl (10.5 mg, 0.0609 mmol, 1.0 eq, as an internal standard for ^{19}F NMR), CD_3CN (0.60 mL) at room temperature (≈23°C) under N_2. After the solution was taken ^{19}F NMR, the solution was returned to a test tube and TsOH·H_2O (11.6 mg, 0.0609 mmol, 1.0 eq) was added to stirred reaction mixtures at room temperature. After 10 min, the solution was directly transferred to a NMR tube again and taken ^{19}F NMR (Figure S4).

The ^{19}F chemical shift of ketone was not changed in the presence of stoichiometric amount of acid.





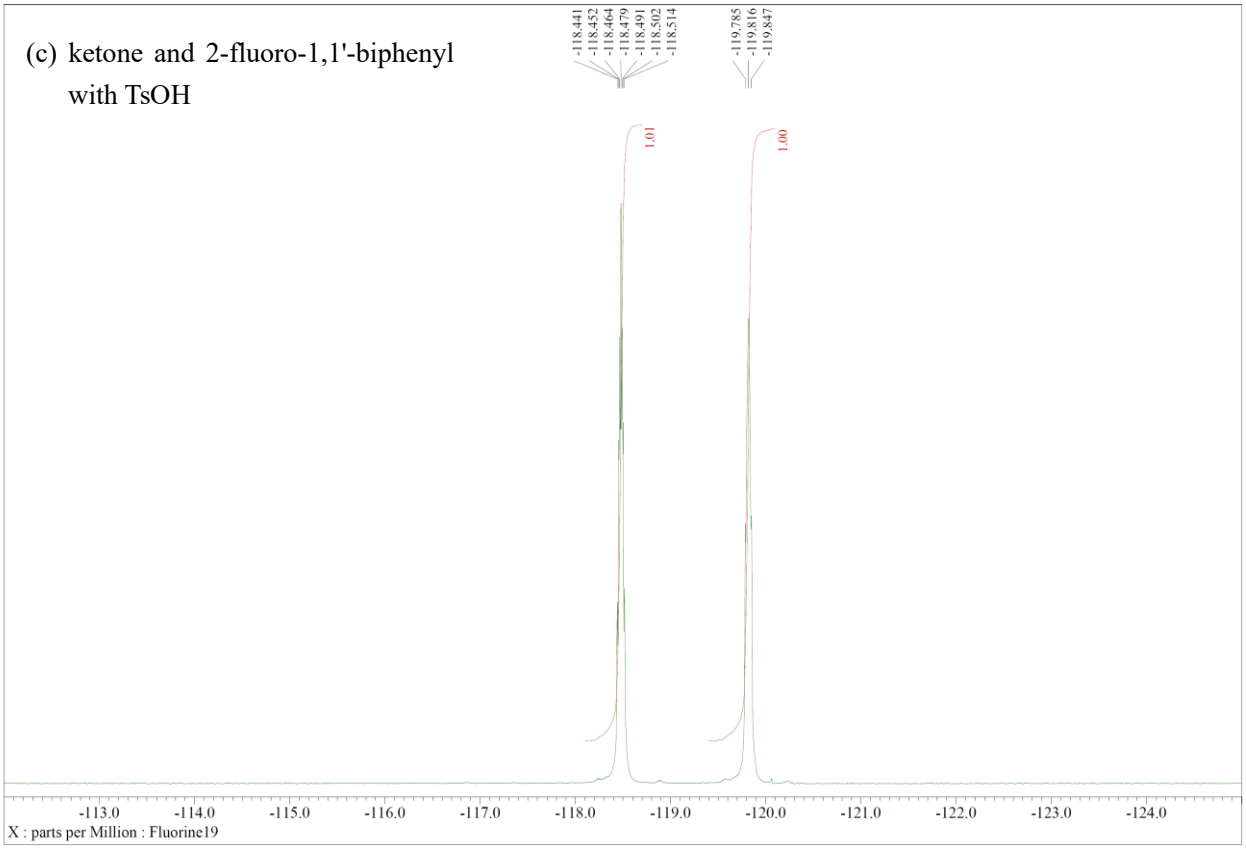
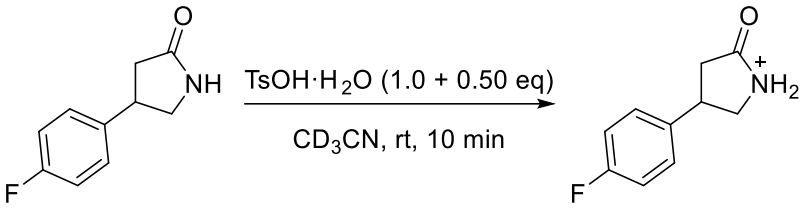


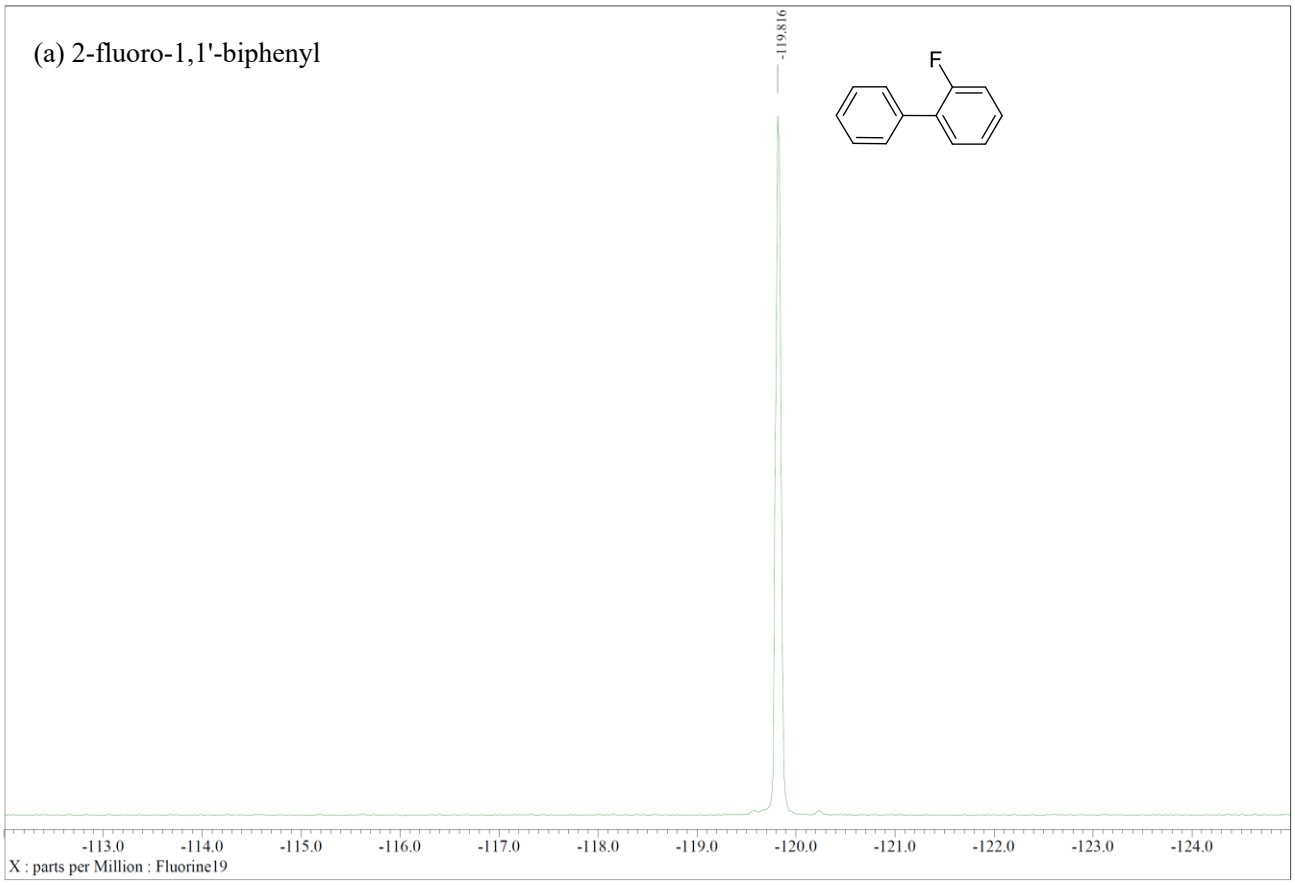
Figure S4. ^{19}F NMR for (a) 2-fluoro-1,1'-biphenyl; (b) ketone and 2-fluoro-1,1'-biphenyl; (c) ketone and 2-fluoro-1,1'-biphenyl with TsOH·H_2O (1.0 eq).

Lactam and acids

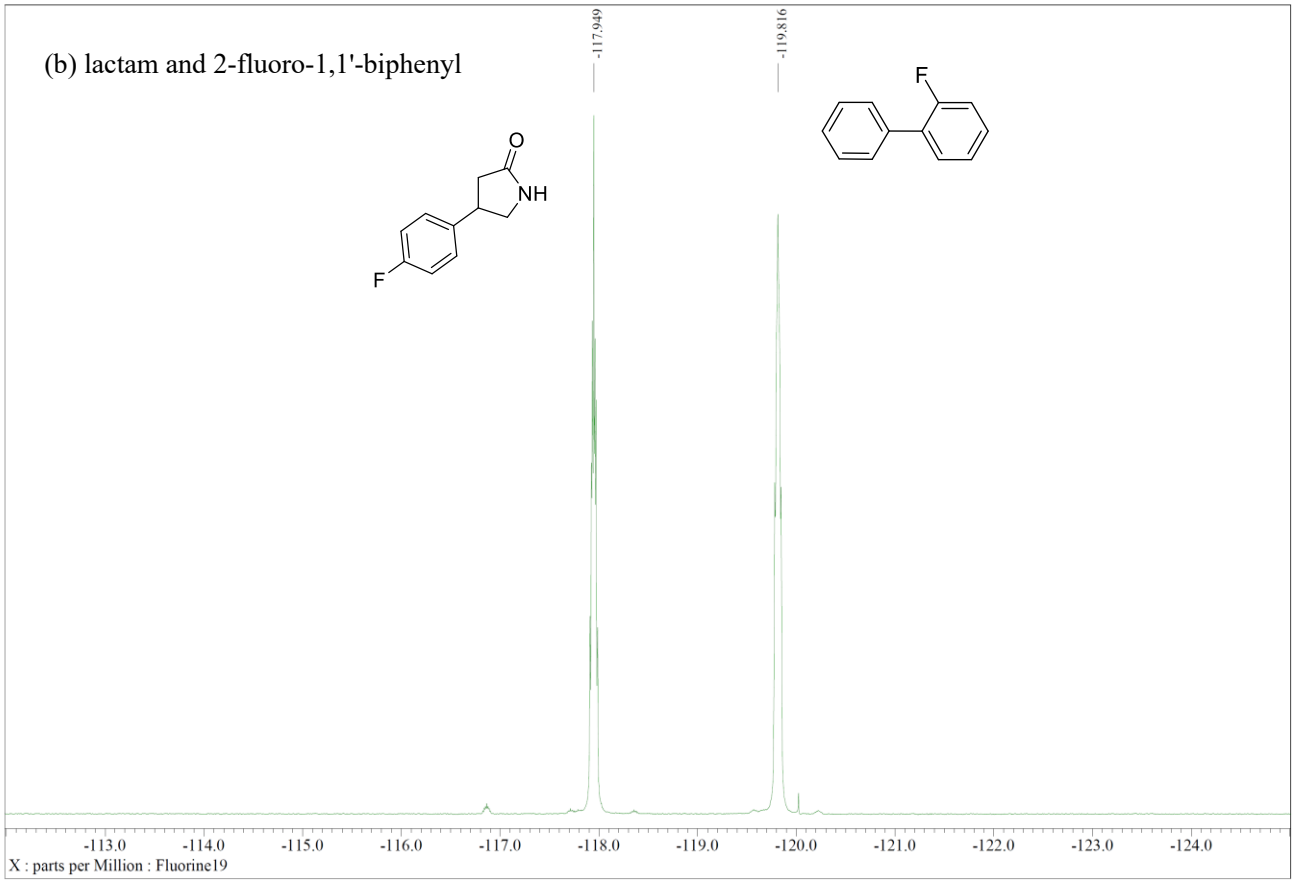


To NMR tube was added to Lactam (10 mg, 0.0558 mmol, 1.0 eq.), 2-fluoro-1,1'-biphenyl (9.6 mg, 0.0558 mmol, 1.0 eq, as an internal standard for ^{19}F NMR), CD_3CN (0.75 mL) at room temperature (≈23°C) under N_2. After the solution was taken ^{19}F NMR, the solution was returned to a test tube and $TsOH·H_2O$ (10.6 mg, 0.0558 mmol, 1.0 eq) was added to stirred reaction mixtures at room temperature. After 10 min, the solution was directly transferred to a NMR tube again and taken ^{19}F NMR. Then, the solution was returned to a test tube and $TsOH·H_2O$ (5.3 mg, 0.0279 mmol, 0.5 eq) was added to stirred reaction mixtures at room temperature. After 10 min, the solution was directly transferred to a NMR tube again and taken ^{19}F NMR (Figure S5).

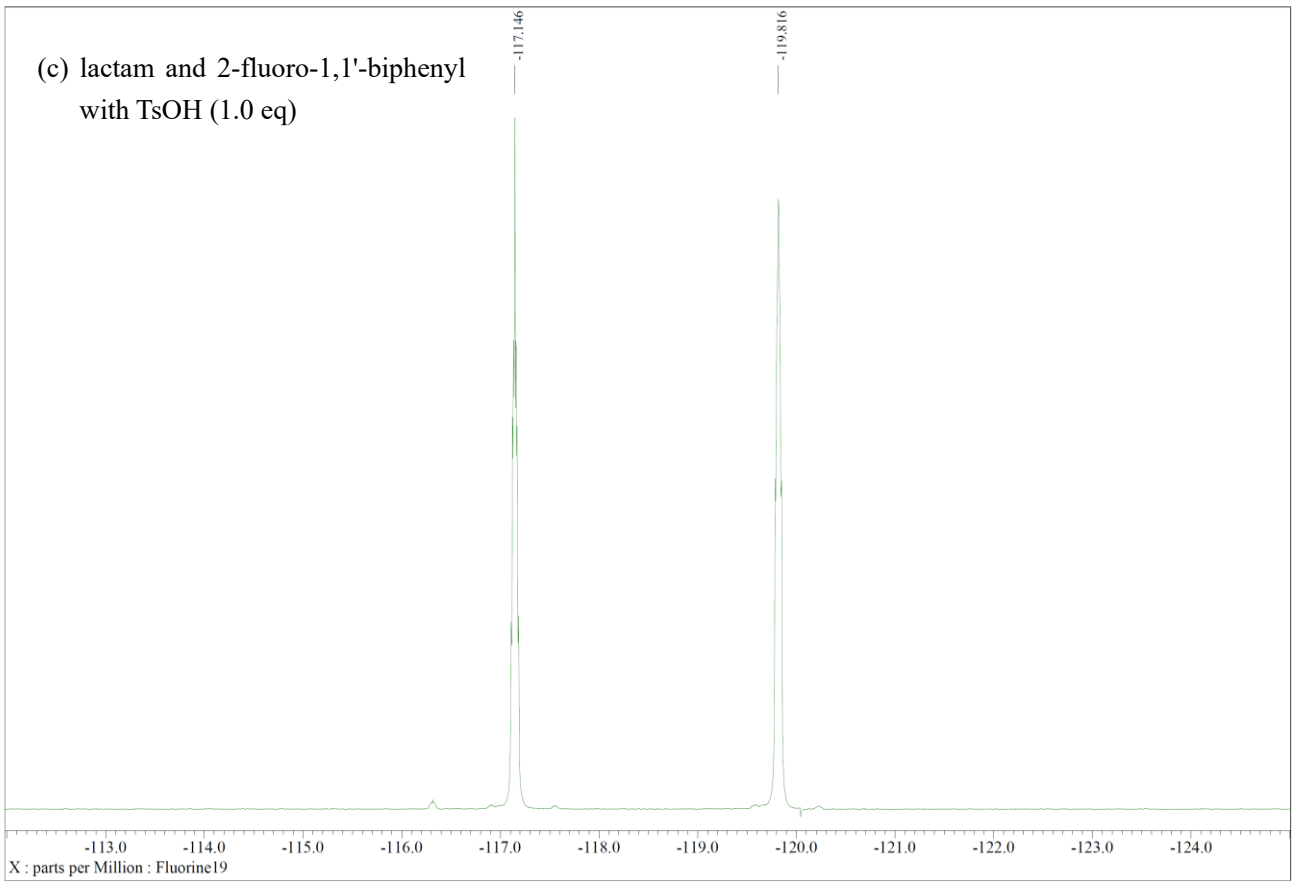
The ^{19}F chemical shift of ketone was changed to downfield as increasing amount of loaded acid.



(b) lactam and 2-fluoro-1,1'-biphenyl



(c) lactam and 2-fluoro-1,1'-biphenyl with TsOH (1.0 eq)



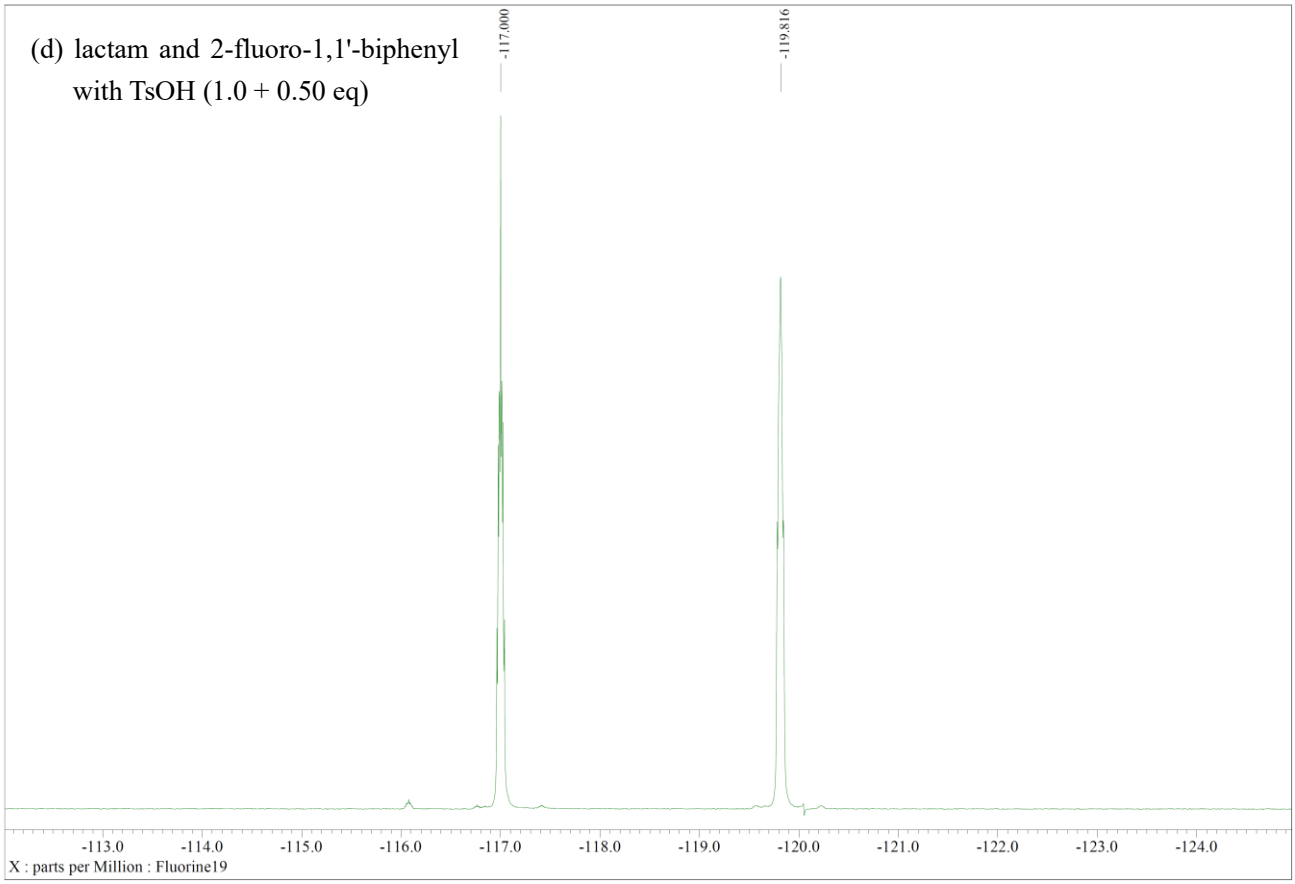
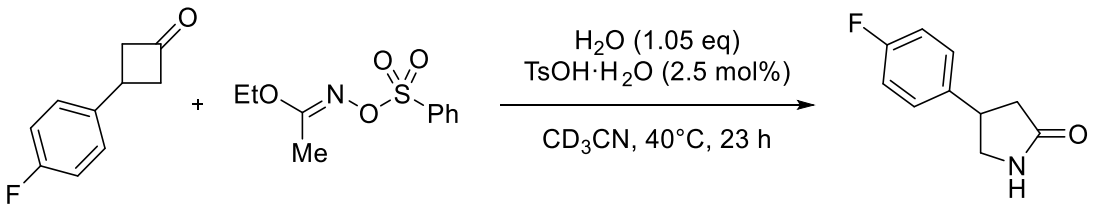


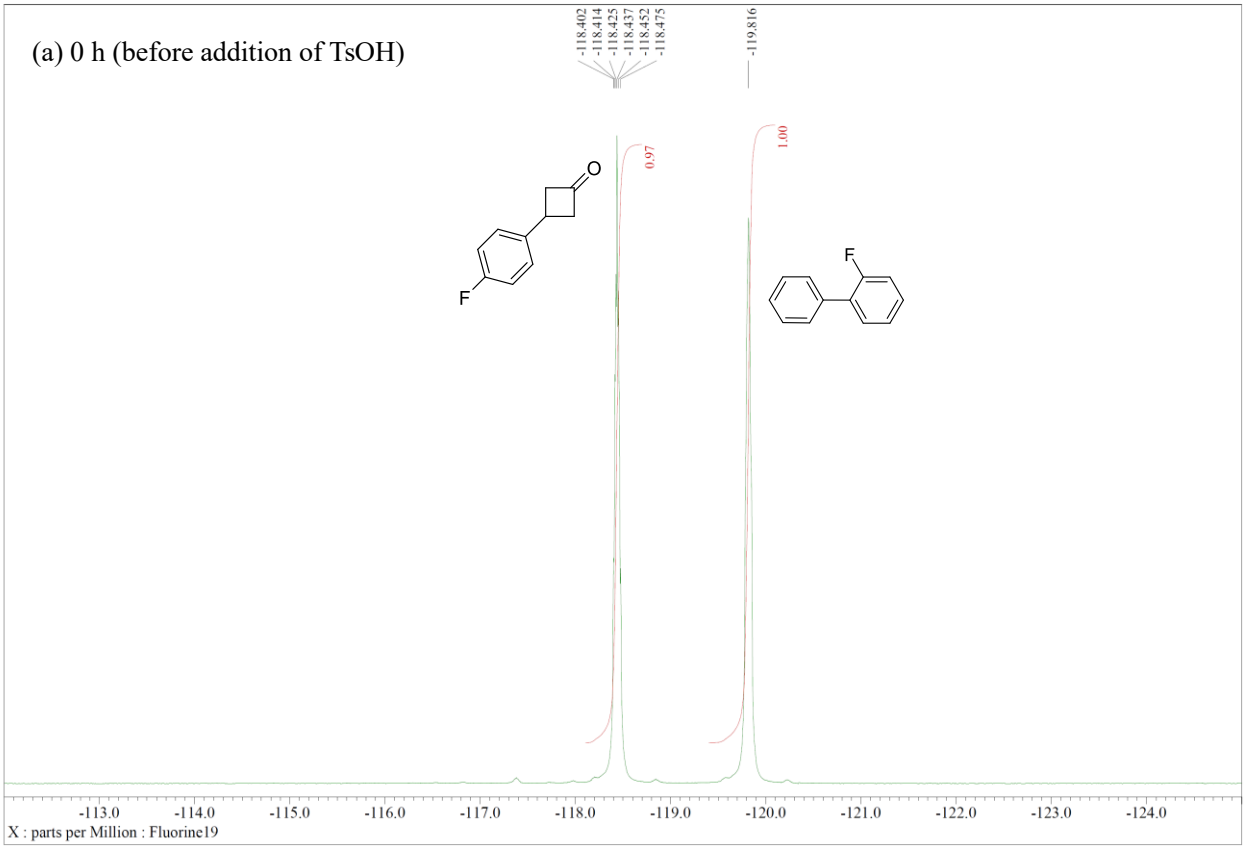
Figure S5. ^{19}F NMR for (a) 2-fluoro-1,1'-biphenyl; (b) lactam and 2-fluoro-1,1'-biphenyl; (c) lactam and 2-fluoro-1,1'-biphenyl with TsOH·H_2O (1.0 eq); (d) lactam and 2-fluoro-1,1'-biphenyl with TsOH·H_2O (1.0 + 0.50 eq).

Observation of reaction behavior in-situ monitored by ^{19}F NMR

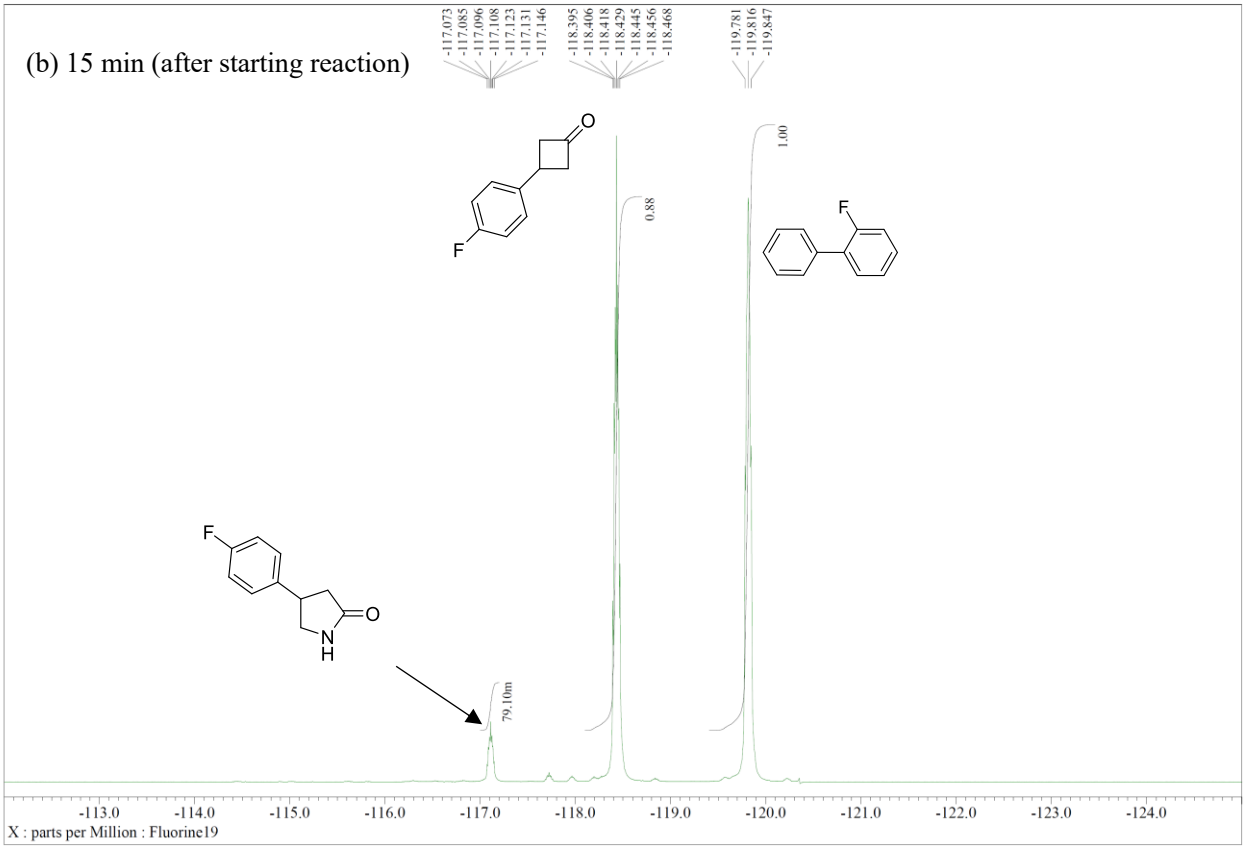


To a test tube was added to ketone (41.0 mg, 0.250 mmol, 1.0 eq.), oxime **2a** (0.300 mmol, 1.2 eq.), 2-fluoro-1,1'-biphenyl (43.1 mg, 0.250 mmol, 1.0 eq, as an internal standard for ^{19}F NMR), CD_3CN (0.75 mL, 0.33 M) at room temperature (≈23°C) under N_2. Then TsOH·H_2O (1.2 mg, 0.00625 mmol, 2.5 mol%) was added to stirred reaction mixtures at room temperature and warmed to 40 ºC. After 15 minutes, the solution was cooling to room temperature and directly transferred to the NMR tube and taken ^{19}F NMR. The solution was returned to the test tube and stirred at 40 ºC again. The same procedure was performed at 0.5, 1, 2, 4, 6, 8, 12, 16, 20 h after the reaction started (Figure S6). The yield was calculated by using internal standard from obtained NMR and plotted graph (Figure S7).

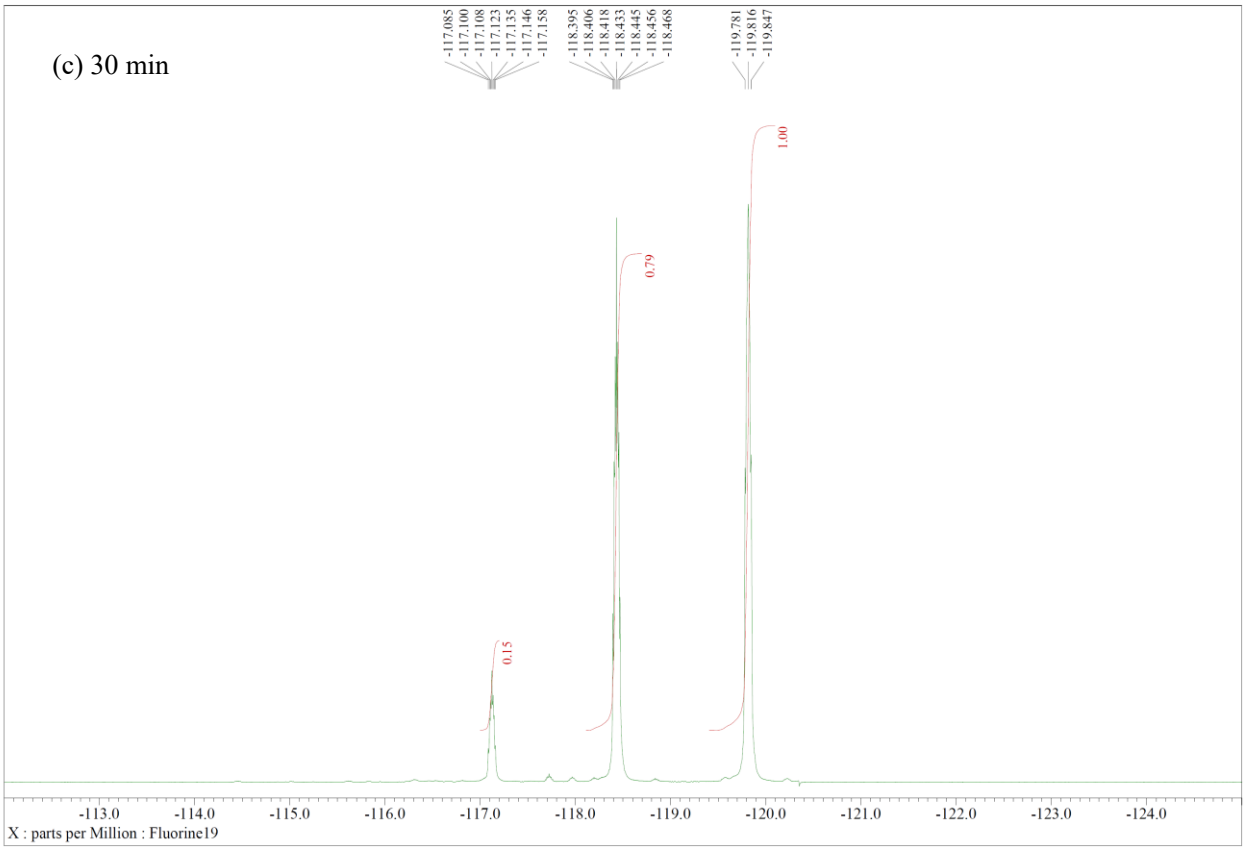
(a) 0 h (before addition of TsOH)



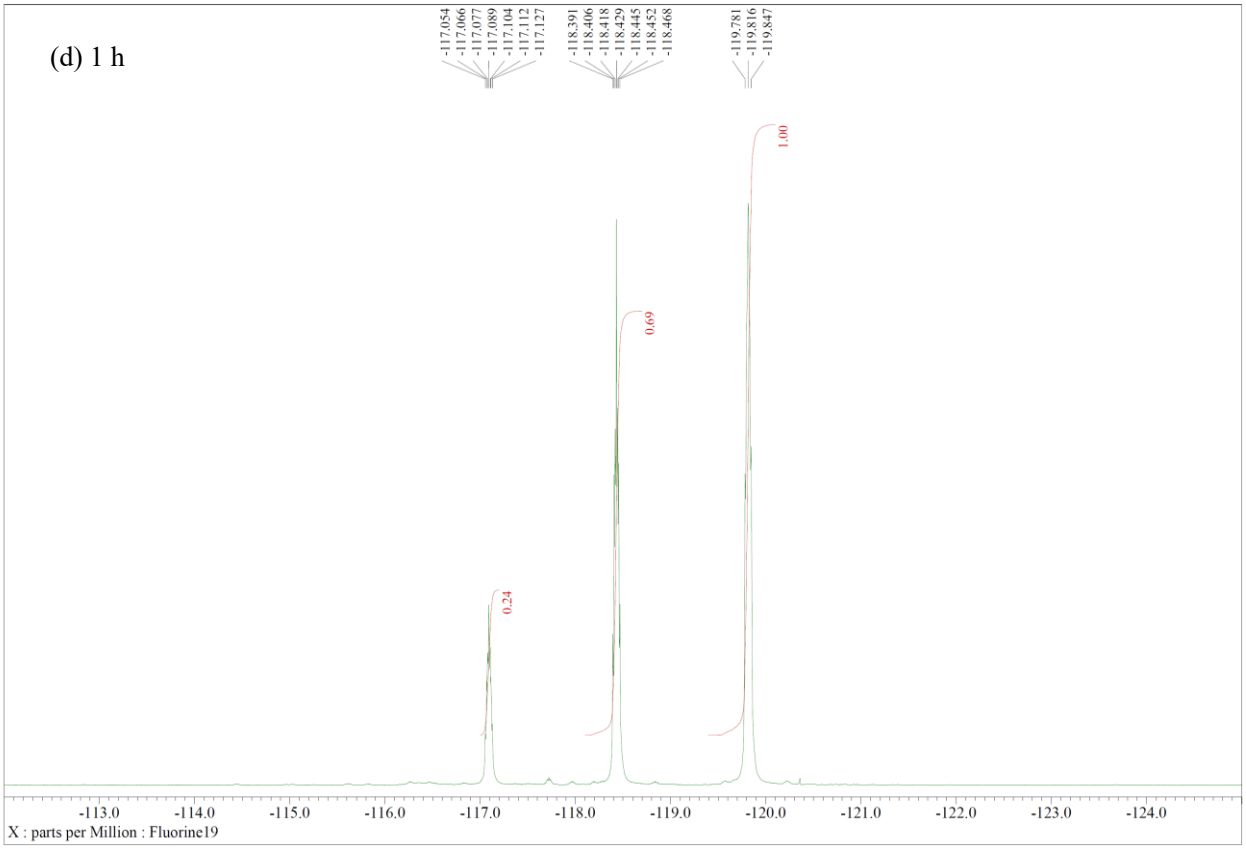
(b) 15 min (after starting reaction)



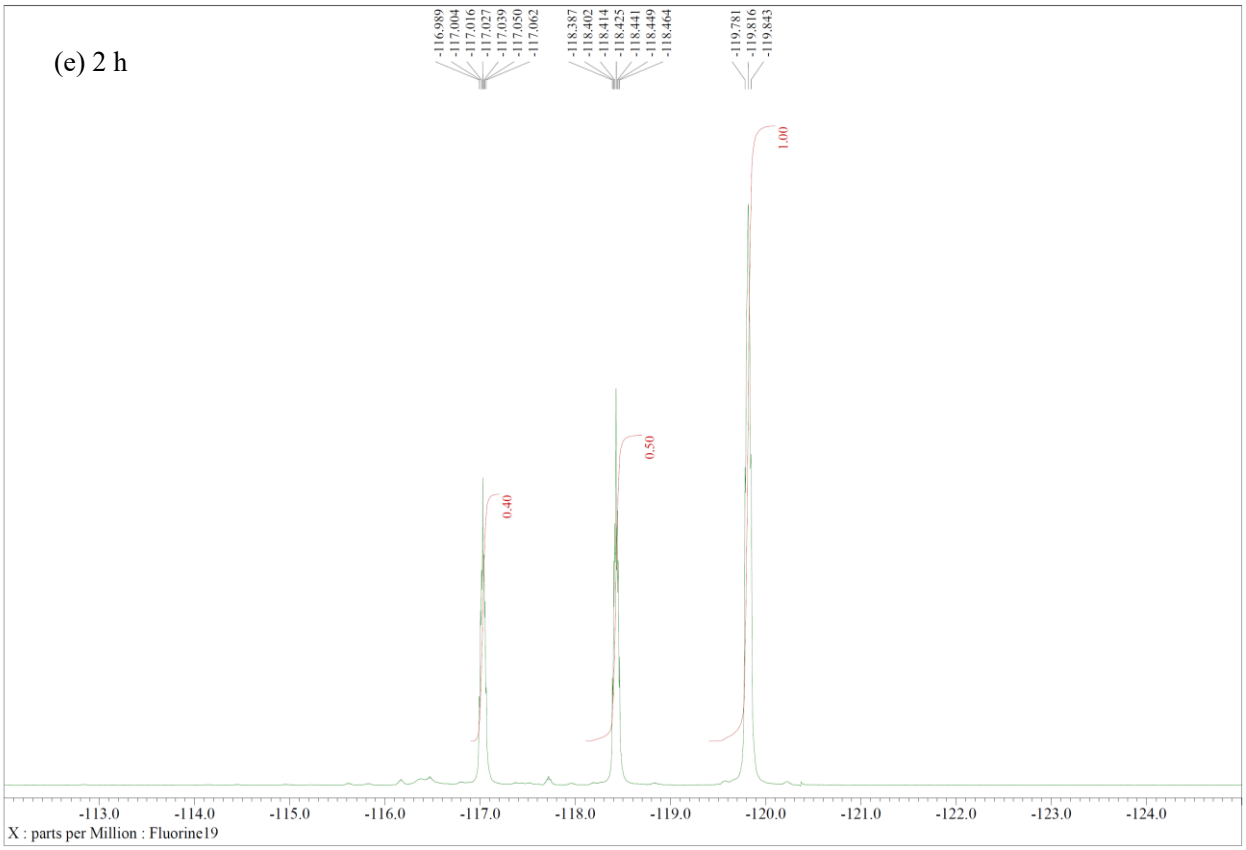
(c) 30 min


-117.085
-117.100
-117.108
-117.123
-117.135
-117.146
-117.158
-118.395
-118.406
-118.418
-118.433
-118.445
-118.456
-118.468
-119.781
-119.816
-119.847
1.00
0.79
0.15
-113.0
-114.0
-115.0
-116.0
-117.0
-118.0
-119.0
-120.0
-121.0
-122.0
-123.0
-124.0
X : parts per Million : Fluorine19

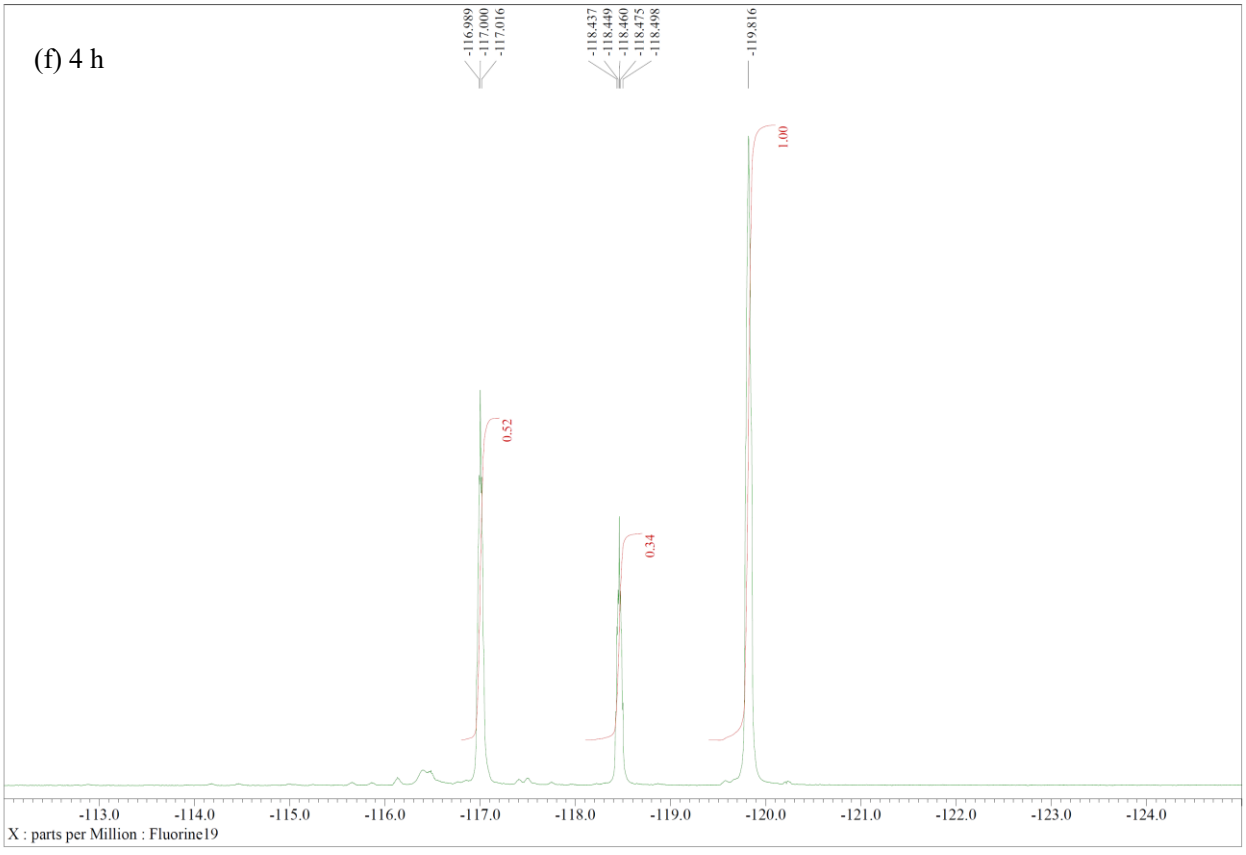
(d) 1 h


-117.054
-117.066
-117.077
-117.089
-117.104
-117.112
-117.127
-118.391
-118.406
-118.418
-118.429
-118.445
-118.452
-118.468
-119.781
-119.816
-119.847
1.00
0.69
0.24
-113.0
-114.0
-115.0
-116.0
-117.0
-118.0
-119.0
-120.0
-121.0
-122.0
-123.0
-124.0
X : parts per Million : Fluorine19

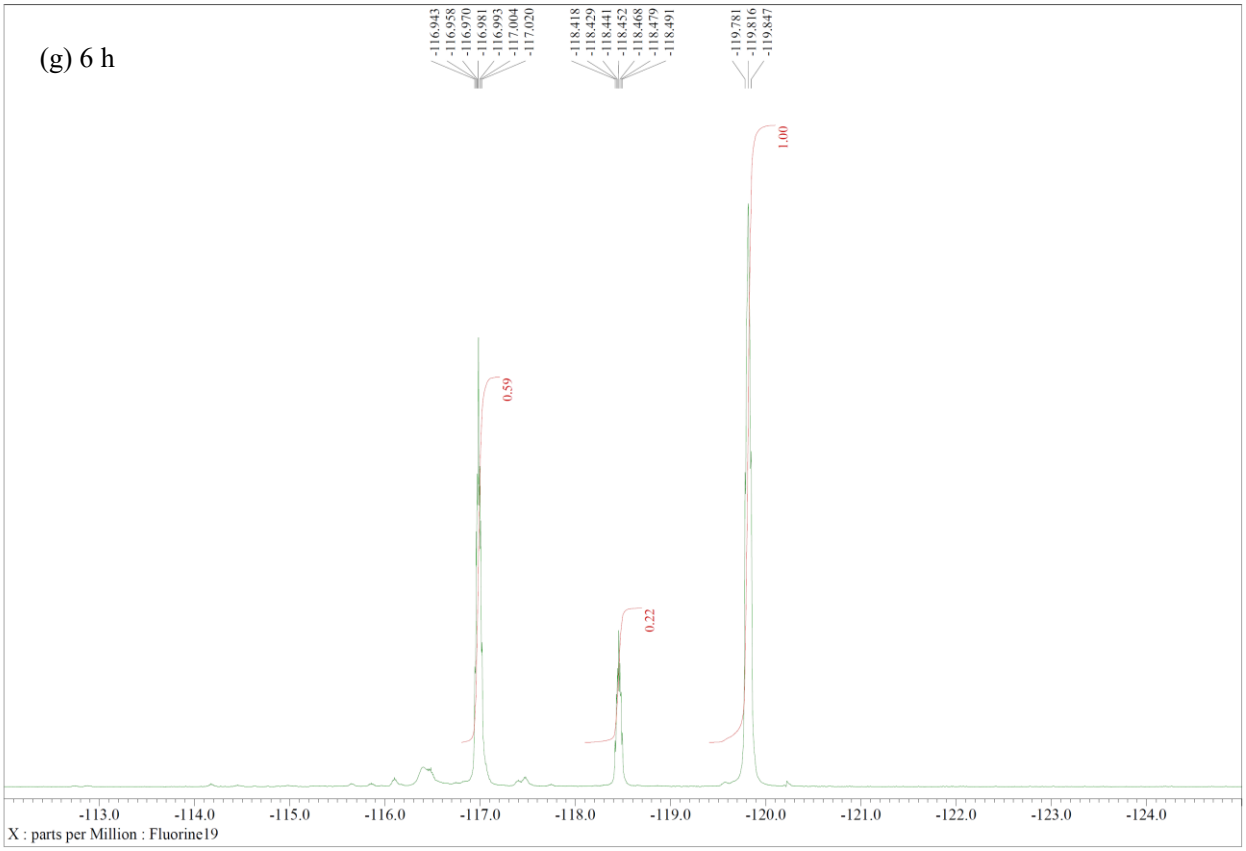
(e) 2 h


-116.989
-117.004
-117.016
-117.027
-117.039
-117.050
-117.062
-118.387
-118.402
-118.414
-118.425
-118.441
-118.449
-118.464
-119.781
-119.816
-119.843
1.00
0.50
0.40
-113.0
-114.0
-115.0
-116.0
-117.0
-118.0
-119.0
-120.0
-121.0
-122.0
-123.0
-124.0
X : parts per Million : Fluorine19

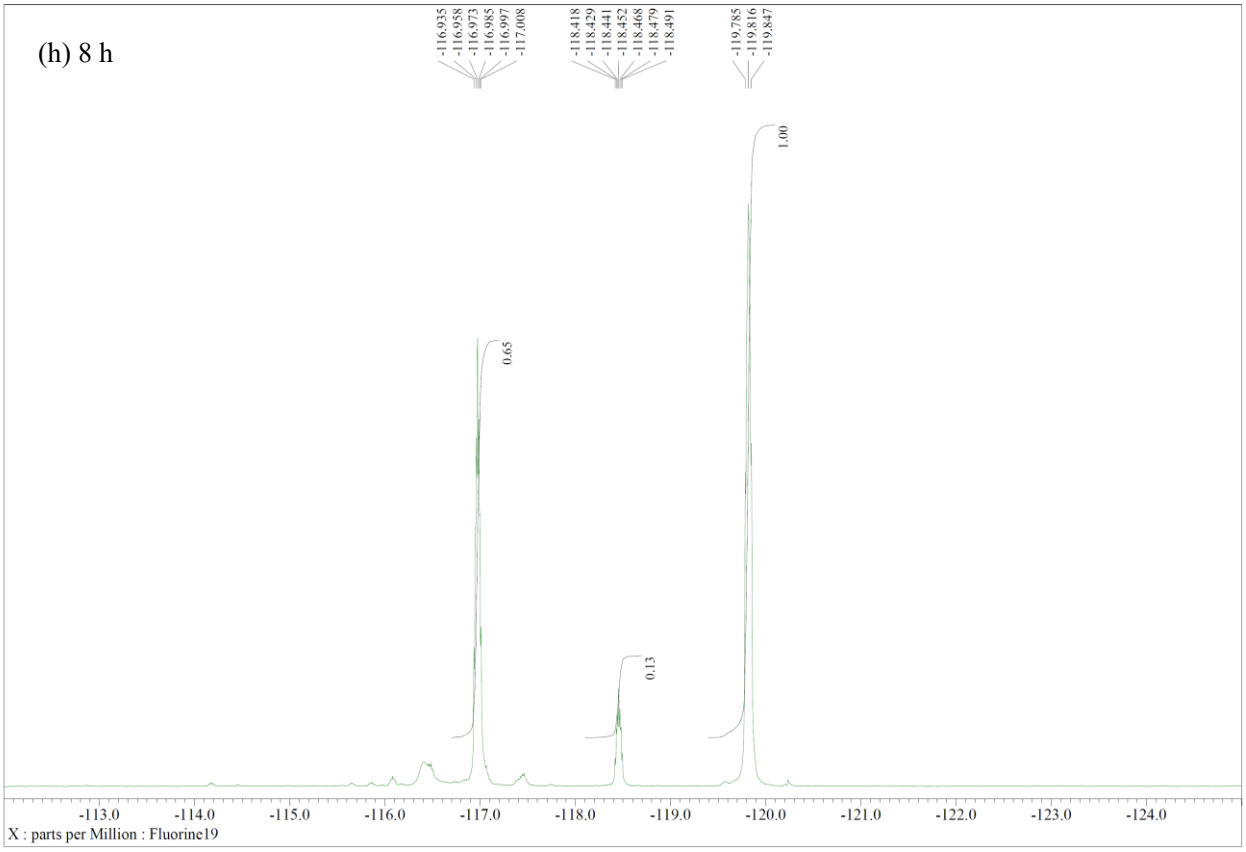
(f) 4 h


-116.989
-117.000
-117.016
-118.437
-118.449
-118.460
-118.475
-118.498
-119.816
1.00
0.52
0.34
-113.0
-114.0
-115.0
-116.0
-117.0
-118.0
-119.0
-120.0
-121.0
-122.0
-123.0
-124.0
X : parts per Million : Fluorine19

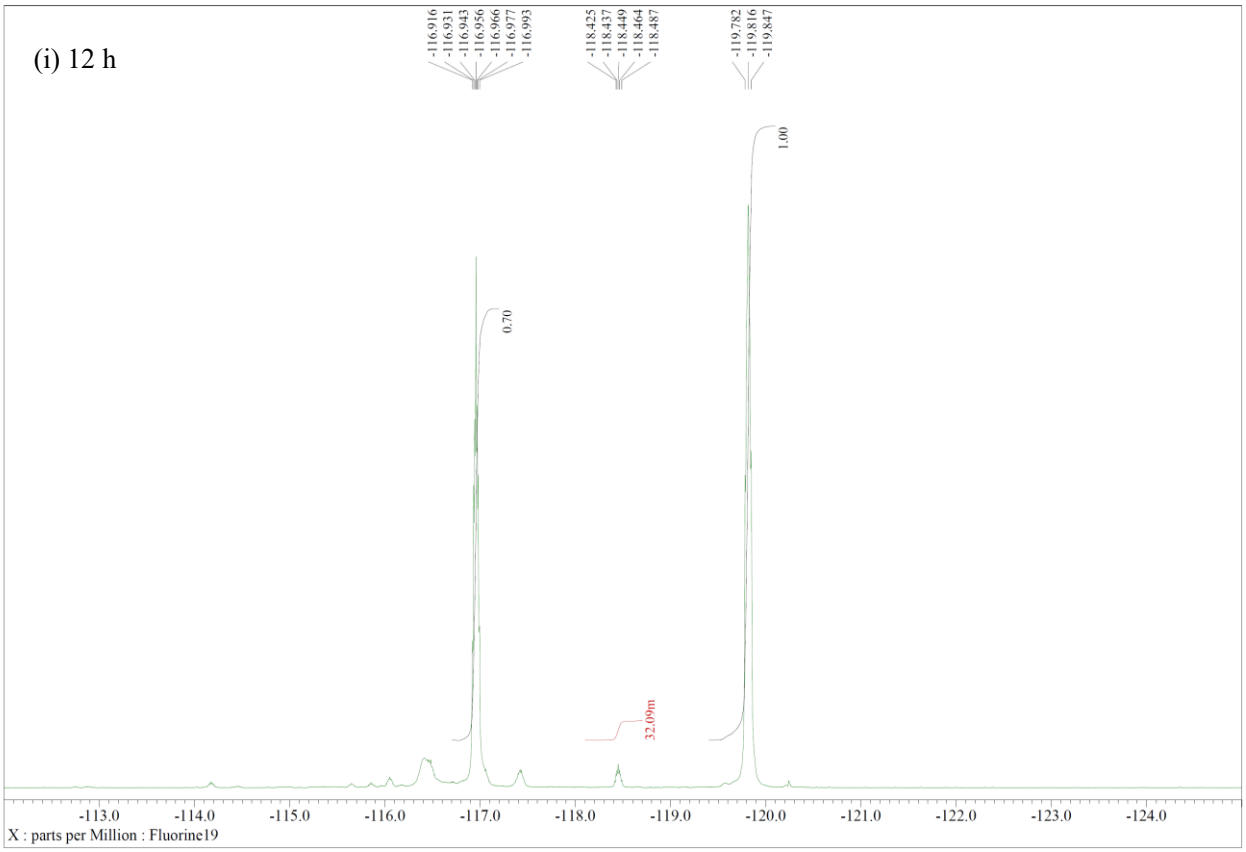
(g) 6 h


-116.943
-116.958
-116.970
-116.981
-116.993
-117.004
-117.020
-118.418
-118.429
-118.441
-118.452
-118.468
-118.479
-118.491
-119.781
-119.816
-119.847
1.00
0.59
0.22
-113.0
-114.0
-115.0
-116.0
-117.0
-118.0
-119.0
-120.0
-121.0
-122.0
-123.0
-124.0
X : parts per Million : Fluorine19

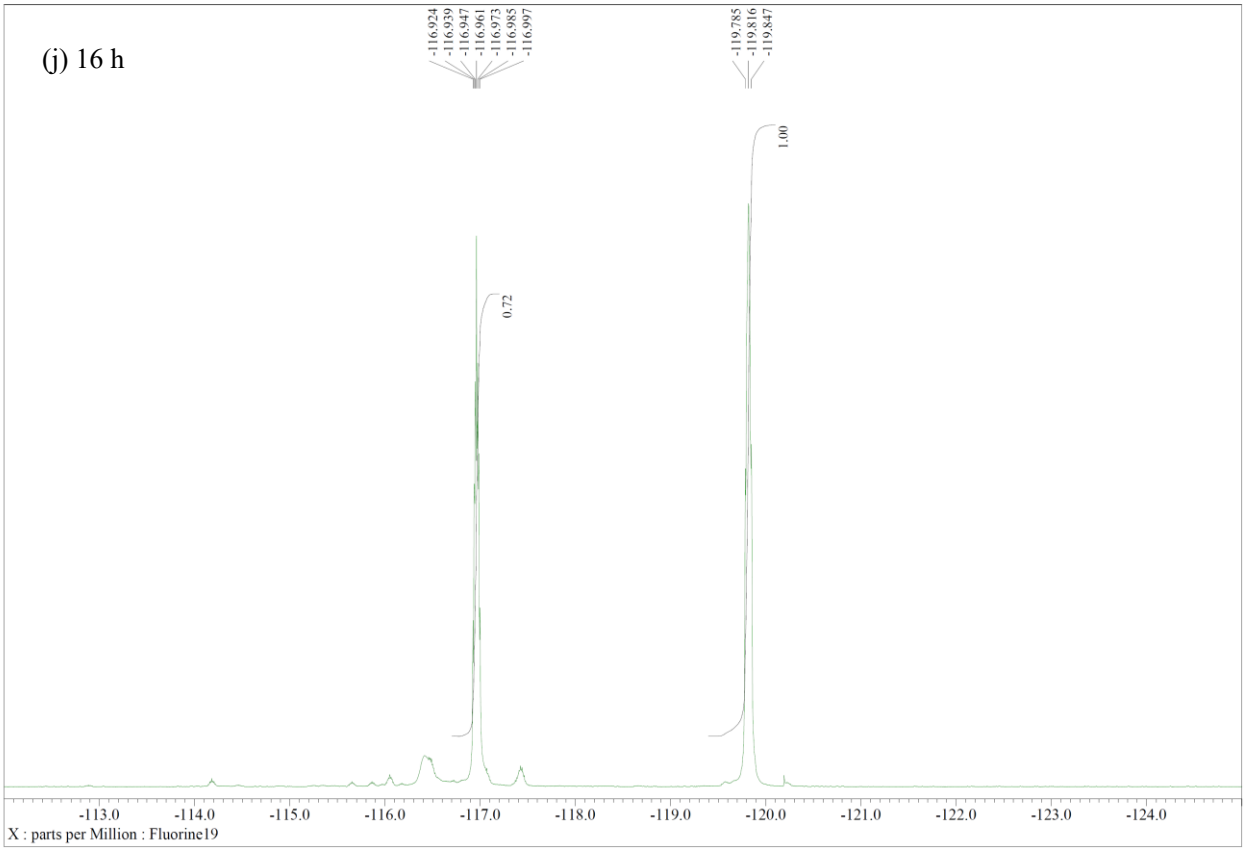
(h) 8 h


-116.935
-116.958
-116.973
-116.985
-116.997
-117.008
-118.418
-118.429
-118.441
-118.452
-118.468
-118.479
-118.491
-119.785
-119.816
-119.847
1.00
0.65
0.13
-113.0
-114.0
-115.0
-116.0
-117.0
-118.0
-119.0
-120.0
-121.0
-122.0
-123.0
-124.0
X : parts per Million : Fluorine19

(i) 12 h


-116.916
-116.931
-116.943
-116.956
-116.966
-116.977
-116.993
-118.425
-118.437
-118.449
-118.464
-118.487
-119.782
-119.816
-119.847
1.00
0.70
32.09m
-113.0
-114.0
-115.0
-116.0
-117.0
-118.0
-119.0
-120.0
-121.0
-122.0
-123.0
-124.0
X : parts per Million : Fluorine19

(j) 16 h


-116.924
-116.939
-116.947
-116.961
-116.973
-116.985
-116.997
-119.785
-119.816
-119.847
1.00
0.72
-113.0
-114.0
-115.0
-116.0
-117.0
-118.0
-119.0
-120.0
-121.0
-122.0
-123.0
-124.0
X : parts per Million : Fluorine19

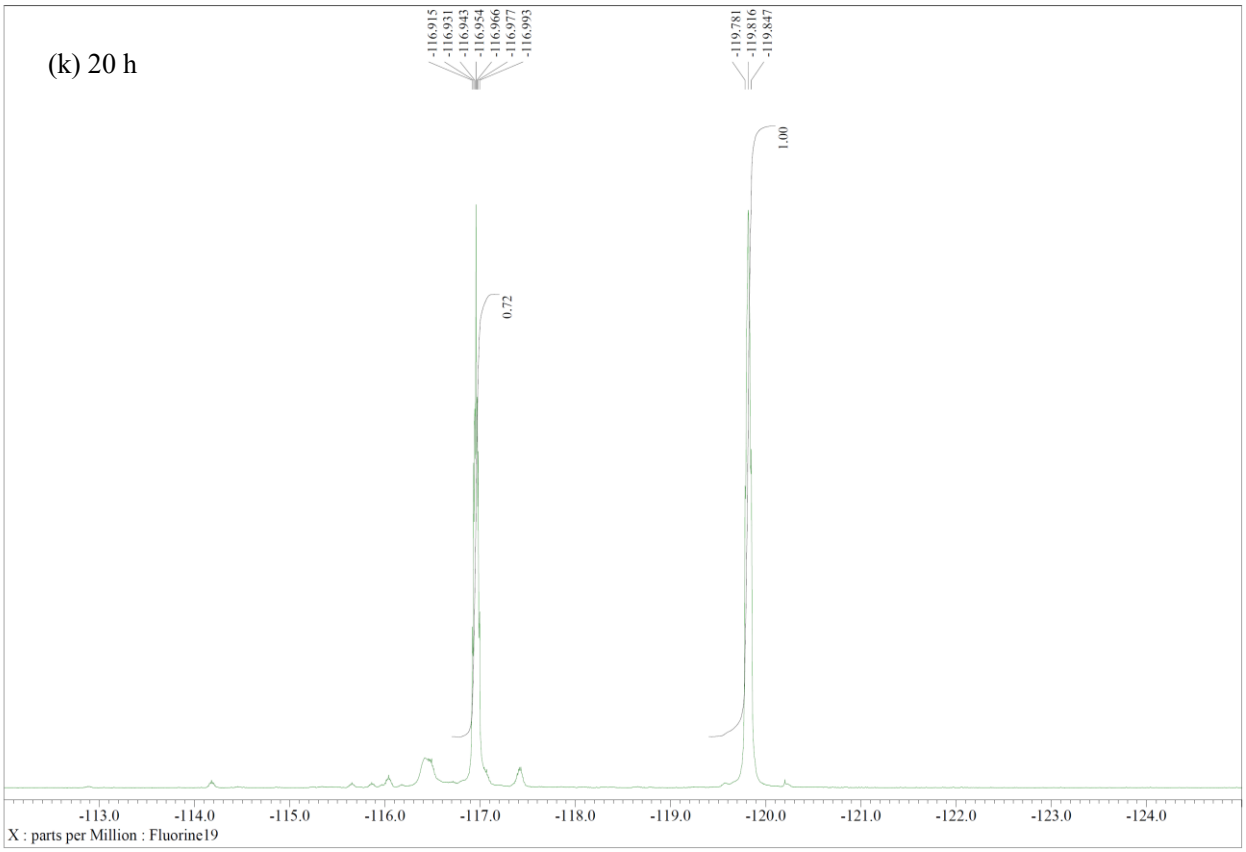


Figure S6. The reaction profile monitored by ^{19}F NMR. (a) 0 h (Before addition of TsOH). (b) 15 min (After the reaction started). (c) 30 min. (d) 1 h. (e) 2 h. (f) 4 h. (g) 6 h. (h) 8 h. (i) 12 h. (j) 16 h. (k) 20 h.

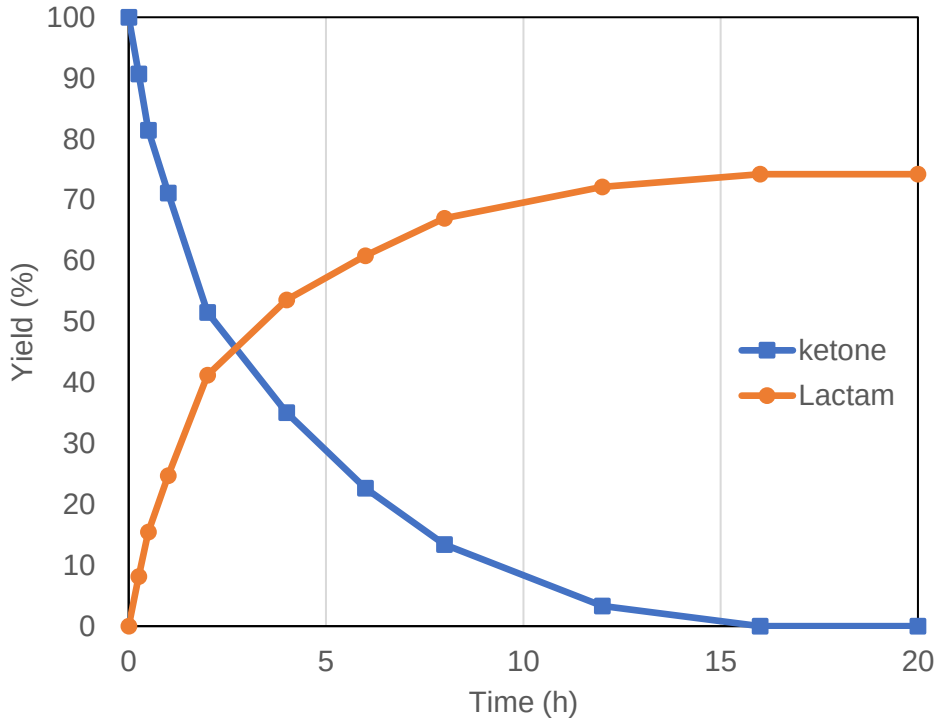
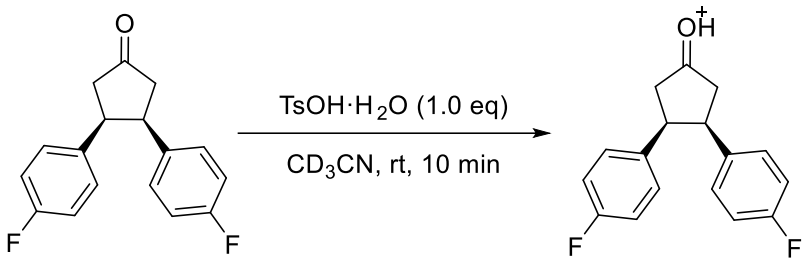


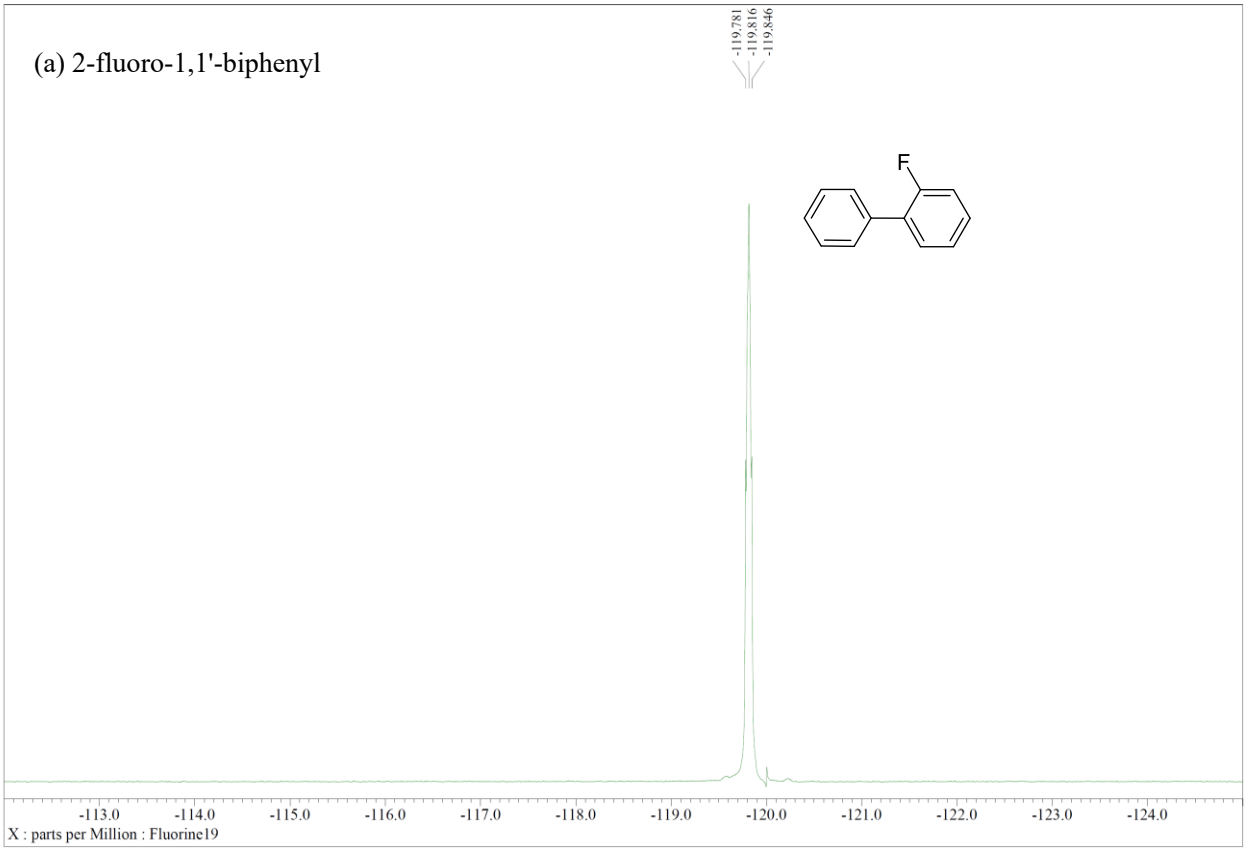
Figure S7. Reaction behavior in-situ (The yields were calculated from ^{19}F NMR using an internal standard).

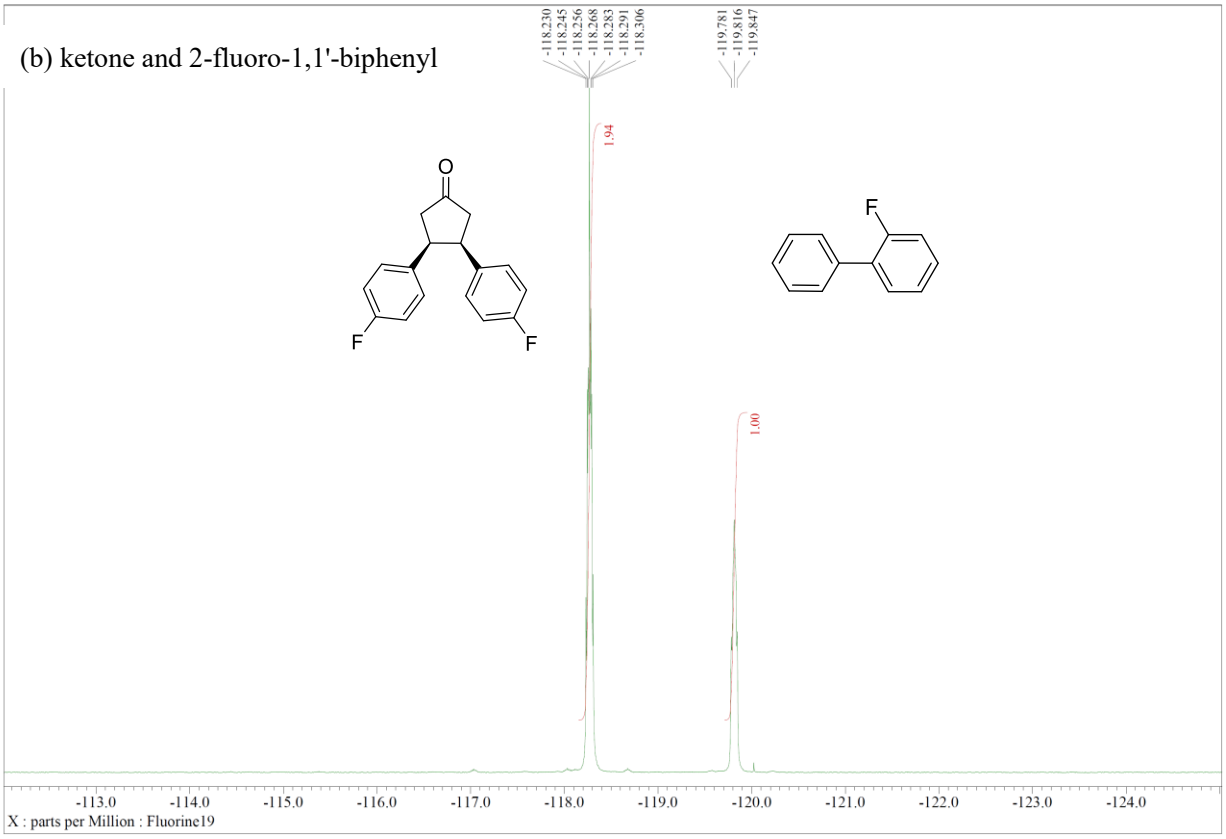
4.6. Observation of reaction behavior using cyclopetanone *in-situ* monitored by ^{19}F NMR

Ketone and acids



To test tube was added to ketone (10 mg, 0.0367 mmol, 1.0 eq.), 2-fluoro-1,1'-biphenyl (6.3 mg, 0.0367 mmol, 1.0 eq, as an internal standard for ^{19}F NMR), CD_3CN (0.60 mL) at room temperature (≈23°C) under N_2. After the solution was taken ^{19}F NMR, the solution was returned to a test tube and $TsOH·H_2O$ (7.0 mg, 0.0367 mmol, 1.0 eq) was added to stirred reaction mixtures at room temperature. After 10 min, the solution was directly transferred to a NMR tube again and taken ^{19}F NMR (Figure S8).





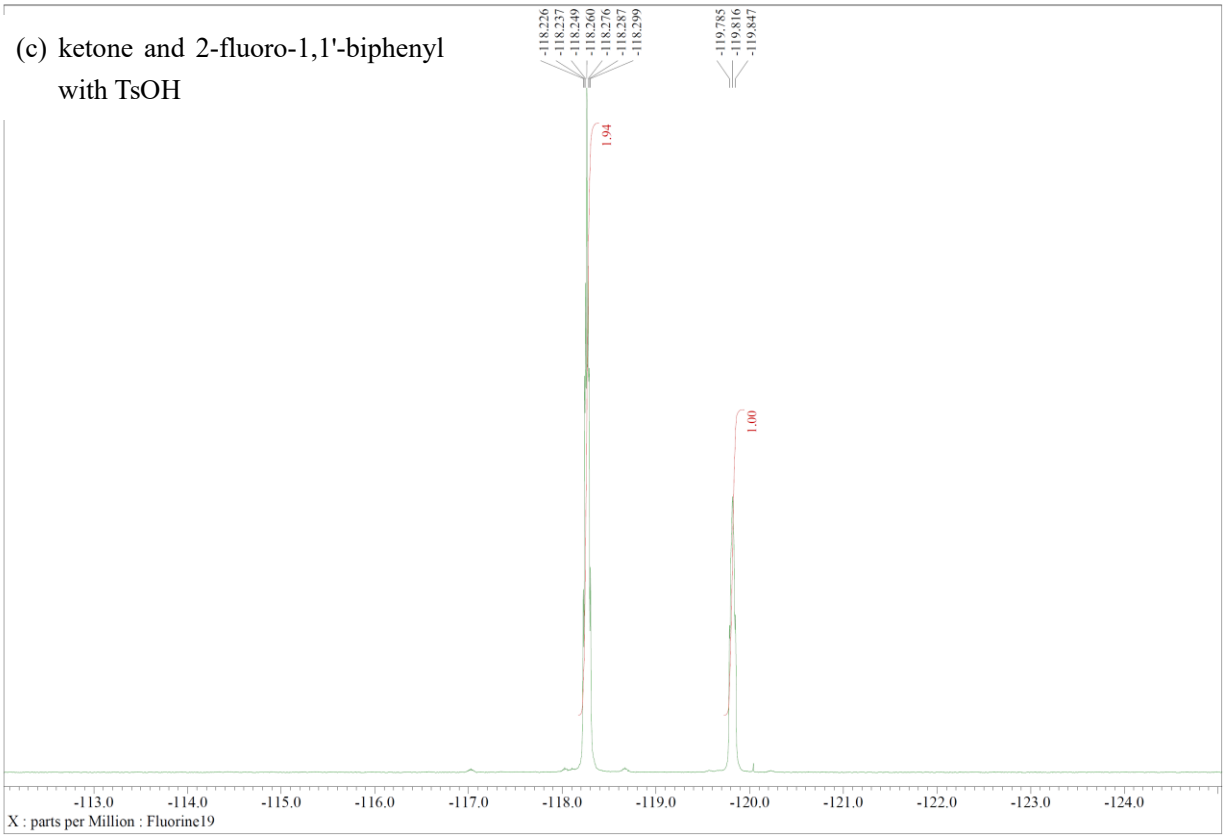
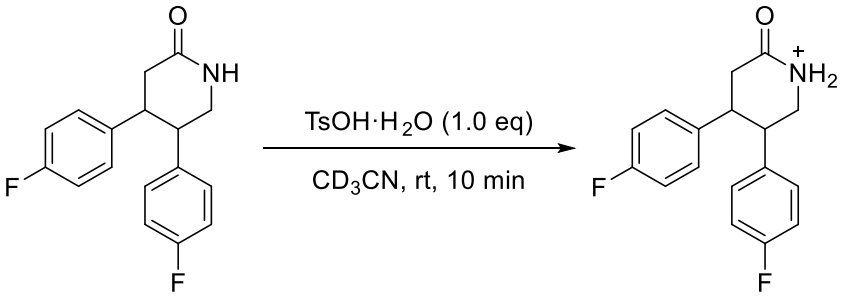
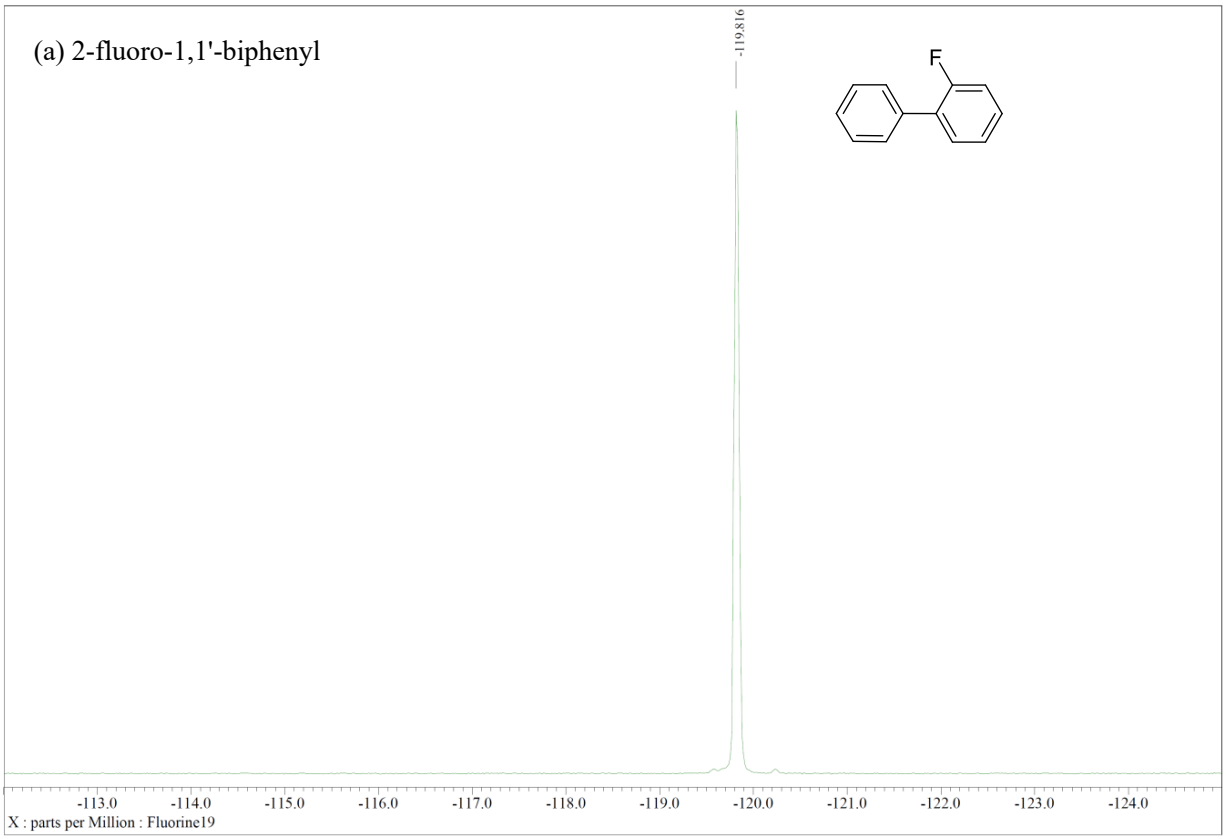


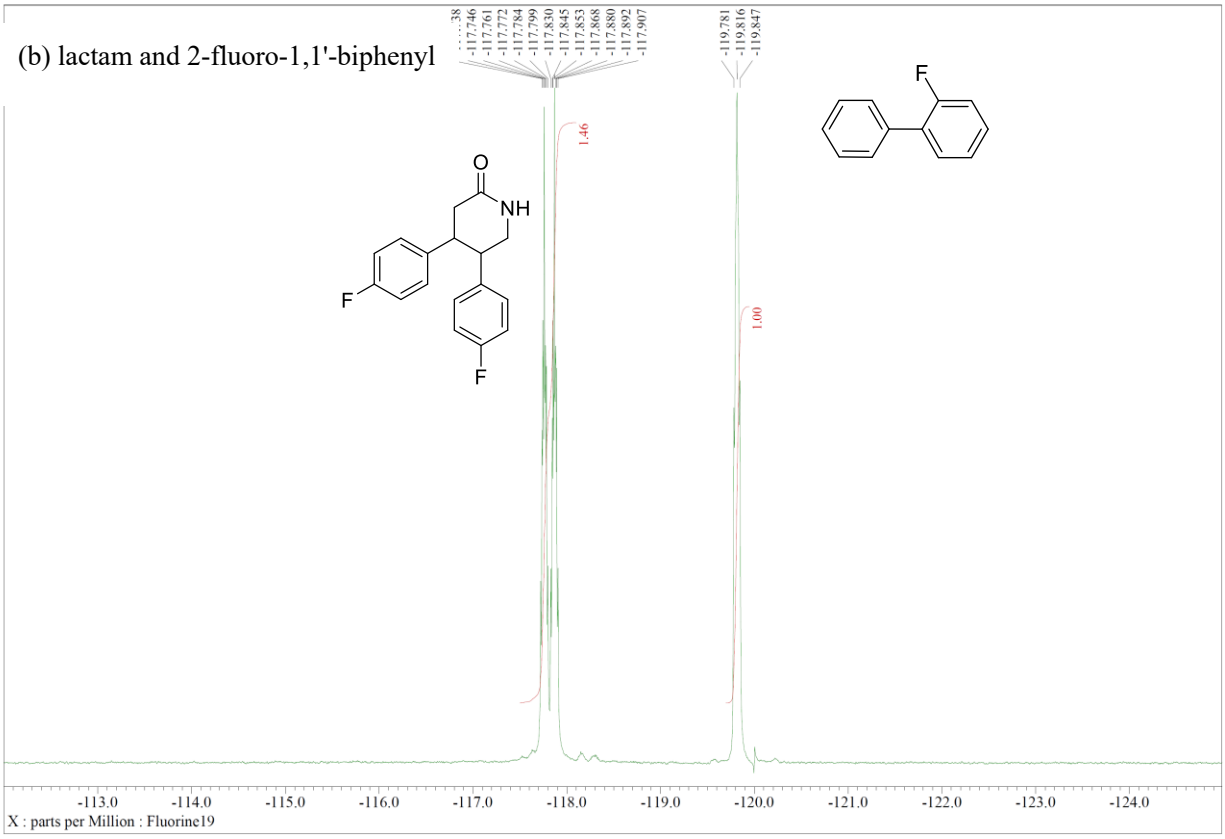
Figure S8. ^{19}F NMR for (a) 2-fluoro-1,1'-biphenyl; (b) ketone and 2-fluoro-1,1'-biphenyl; (c) ketone and 2-fluoro-1,1'-biphenyl with TsOH·H_2O (1.0 eq).

Lactam and acids



To test tube was added to lactam (8.0 mg, 0.0348 mmol, 1.0 eq.), 2-fluoro-1,1'-biphenyl (4.8 mg, 0.0348 mmol, 1.0 eq, as an internal standard for ^{19}F NMR), CD_3CN (0.60 mL) at room temperature (≈23°C) under N_2. After the solution was taken ^{19}F NMR, the solution was returned to a test tube and $TsOH·H_2O$ (5.3 mg, 0.0348 mmol, 1.0 eq) was added to stirred reaction mixtures at room temperature. After 10 min, the solution was directly transferred to a NMR tube again and taken ^{19}F NMR (Figure S9).





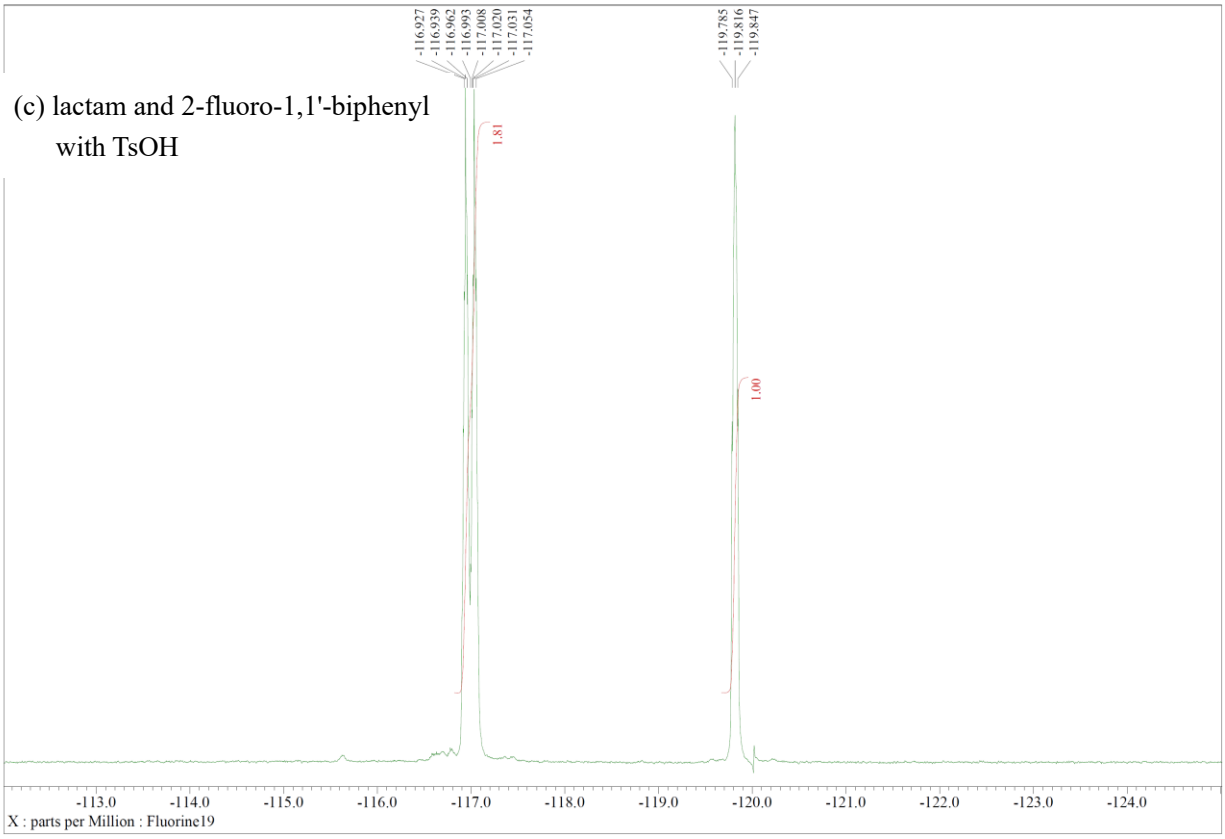
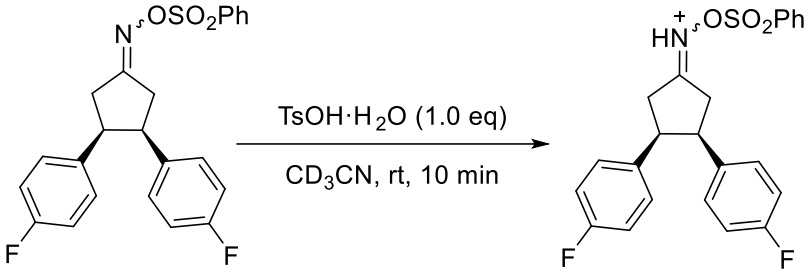
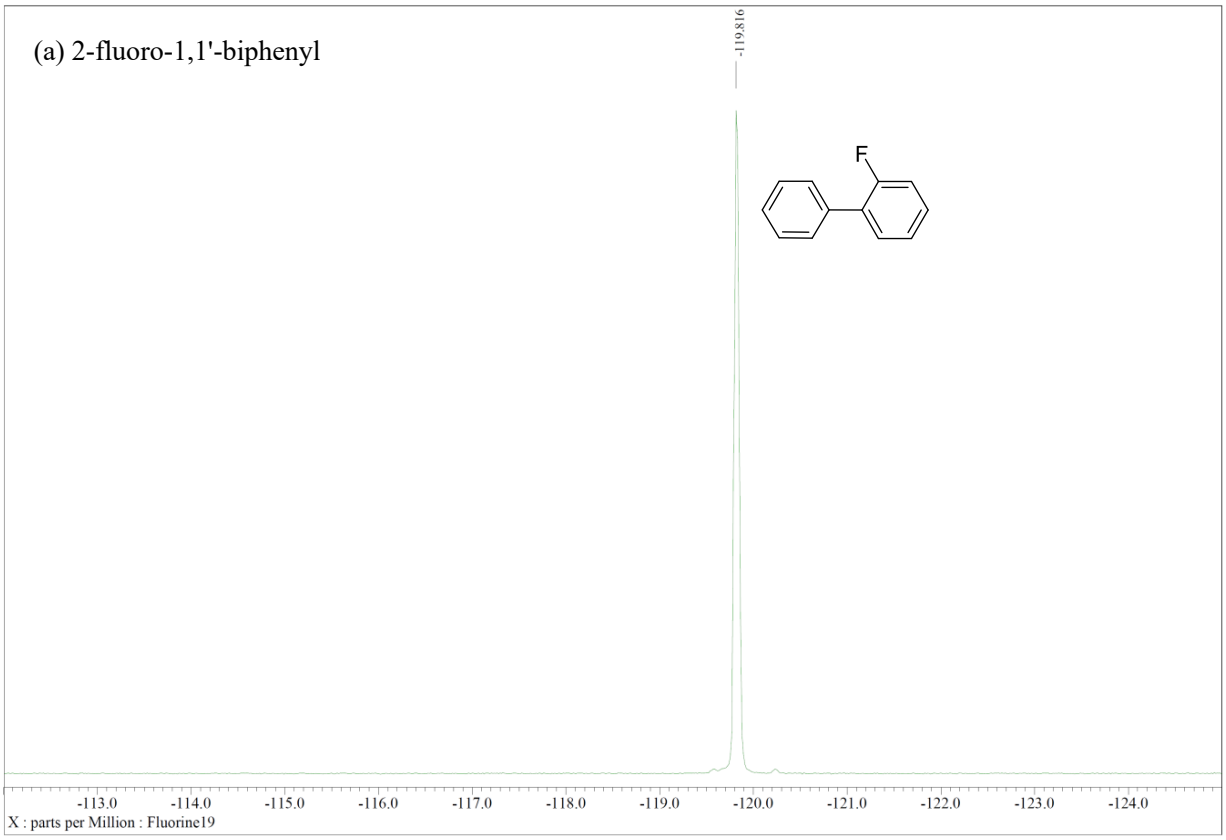


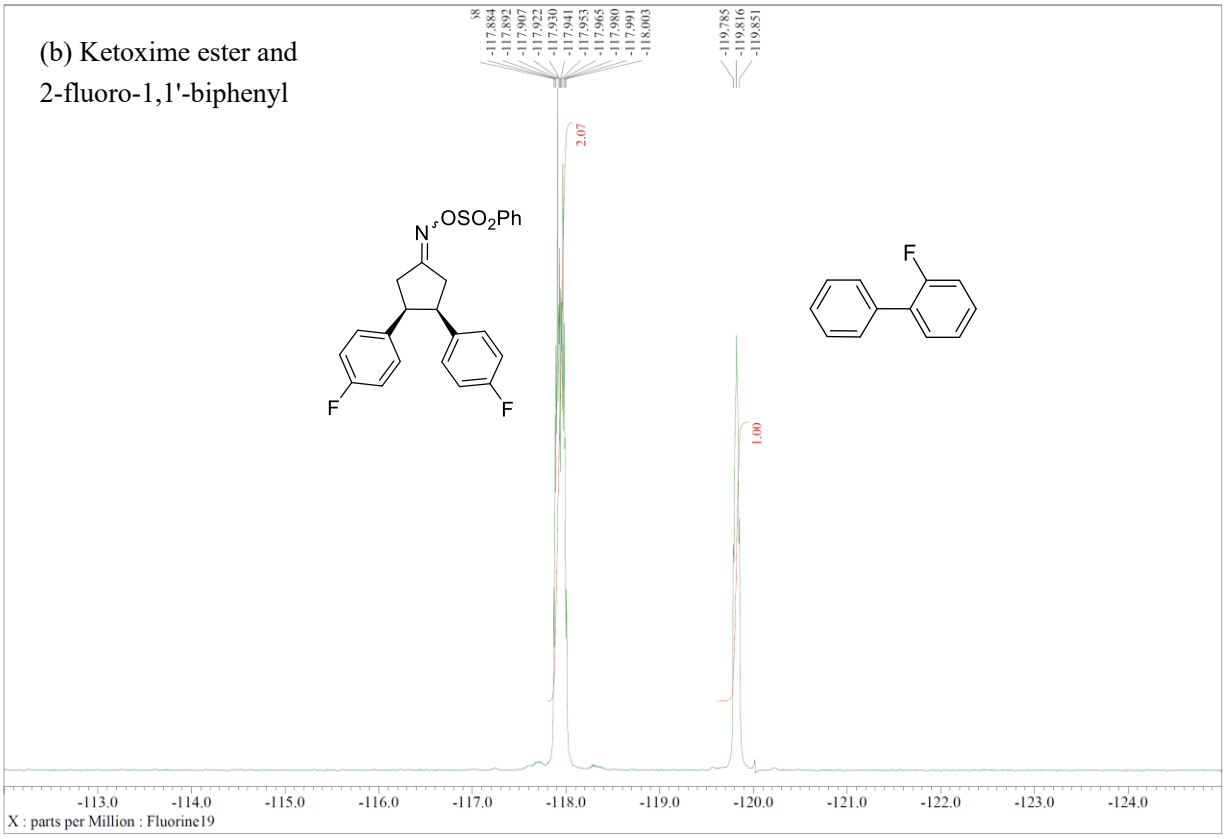
Figure S9. ^{19}F NMR for (a) 2-fluoro-1,1'-biphenyl; (b) lactam and 2-fluoro-1,1'-biphenyl; (c) lactam and 2-fluoro-1,1'-biphenyl with TsOH·H_2O (1.0 eq).

Ketoxime ester and acids



To test tube was added to ketoxime ester (10 mg, 0.0234 mmol, 1.0 eq.), 2-fluoro-1,1'-biphenyl (4.0 mg, 0.0234 mmol, 1.0 eq, as an internal standard for ^{19}F NMR), CD_3CN (0.60 mL) at room temperature (≈23°C) under N_2. After the solution was taken ^{19}F NMR, the solution was returned to a test tube and $TsOH·H_2O$ (4.4 mg, 0.0234 mmol, 1.0 eq) was added to stirred reaction mixtures at room temperature. After 10 min, the solution was directly transferred to a NMR tube again and taken ^{19}F NMR (Figure S10).





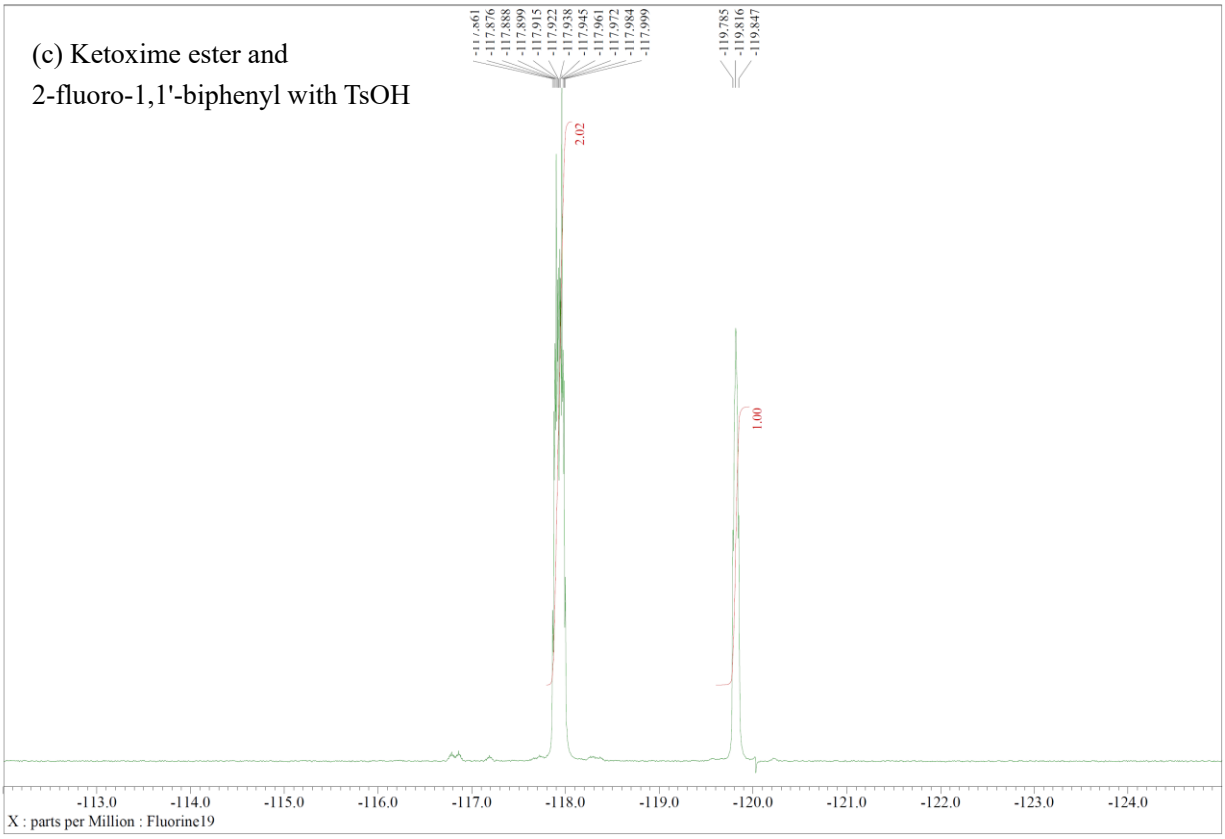
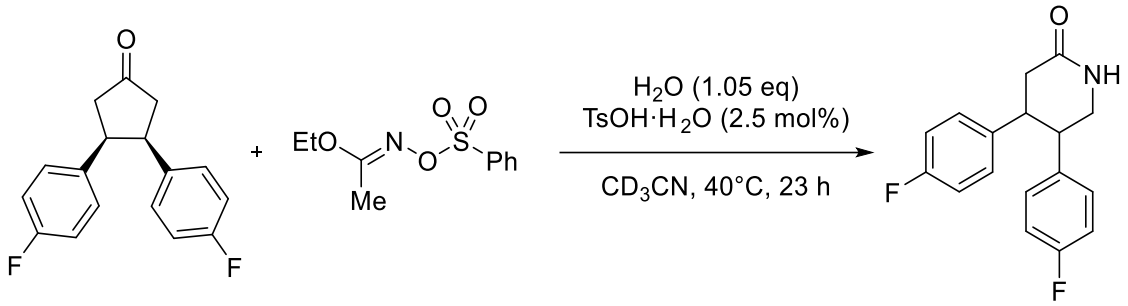
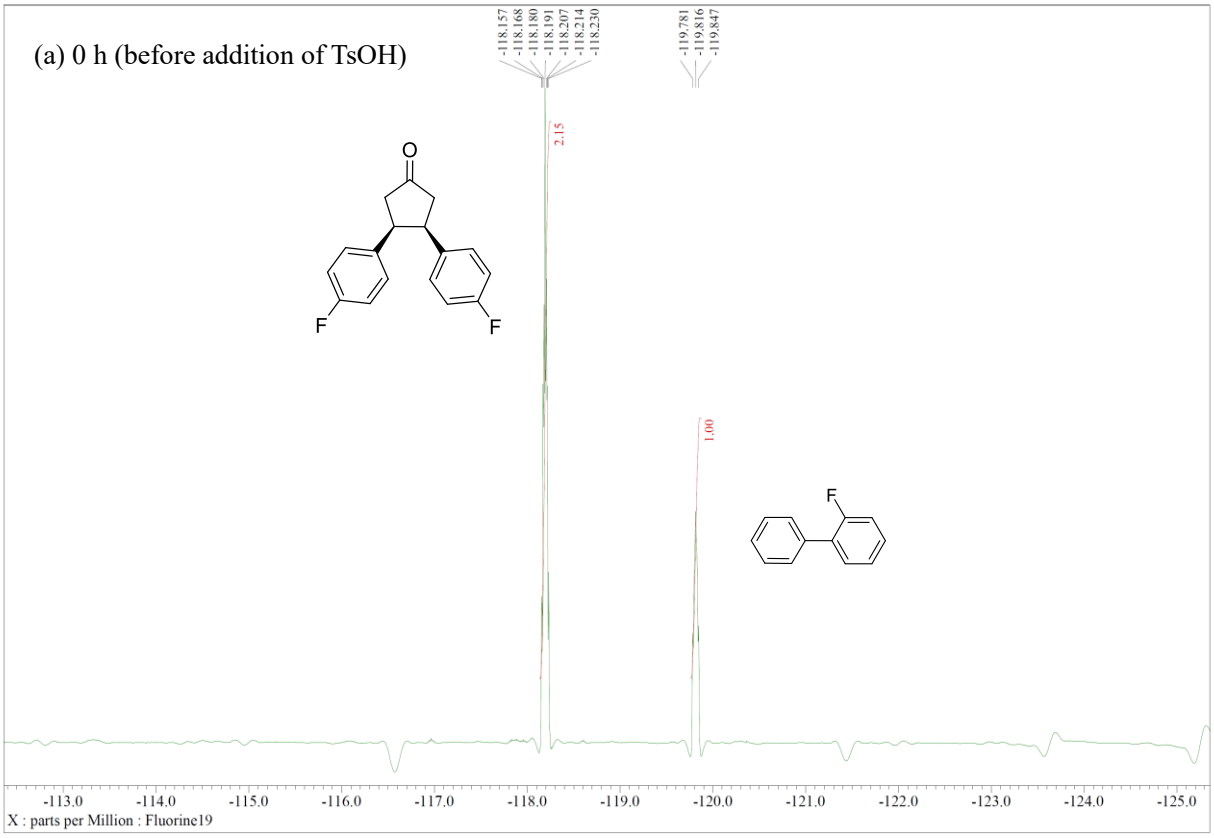


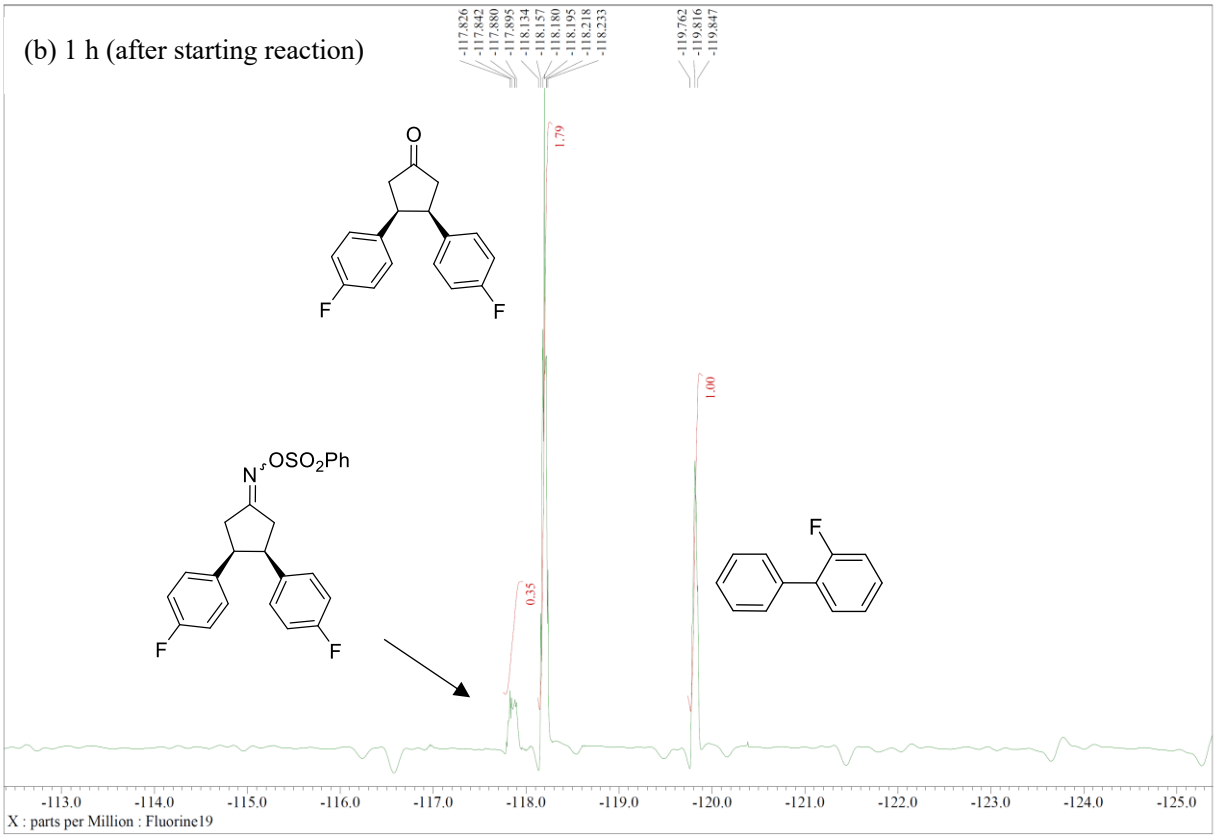
Figure S10. ^{19}F NMR for (a) 2-fluoro-1,1'-biphenyl; (b) ketoxime ester and 2-fluoro-1,1'-biphenyl; (c) ketoxime ester and 2-fluoro-1,1'-biphenyl with TsOH·H_2O (1.0 eq).

Observation of reaction behavior *in-situ* monitored by ^{19}F NMR



To a test tube was added to ketone (68.1 mg, 0.250 mmol, 1.0 eq.), oxime **2a** (73.0 mg, 0.300 mmol, 1.2 eq.), 2-fluoro-1,1'-biphenyl (43.1 mg, 0.250 mmol, 1.0 eq, as an internal standard for ^{19}F NMR), CD_3CN (0.75 mL, 0.33 M) at room temperature (≈23°C) under N_2. Then $TsOH{\cdot}H_2O$ (2.4 mg, 0.0125 mmol, 5.0 mol%) was added to stirred reaction mixtures at room temperature and warmed to 40 ºC. After 1 hour, the solution was cooling to room temperature and directly transferred to the NMR tube and taken ^{19}F NMR. The solution was returned to the test tube and stirred at 40 ºC again. The same procedure was performed at 2, 8, 22 h after the reaction started (Figure S11). From these results, we found ketoxime ester was observed reaction *in-situ*.




(b) 1 h (after starting reaction)
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-117.842
-117.880
-117.895
-118.134
-118.157
-118.180
-118.195
-118.218
-118.233
-119.762
-119.816
-119.847
1.79
1.00
0.35
O
F
F
N
OSO2Ph
F
F
-113.0
-114.0
-115.0
-116.0
-117.0
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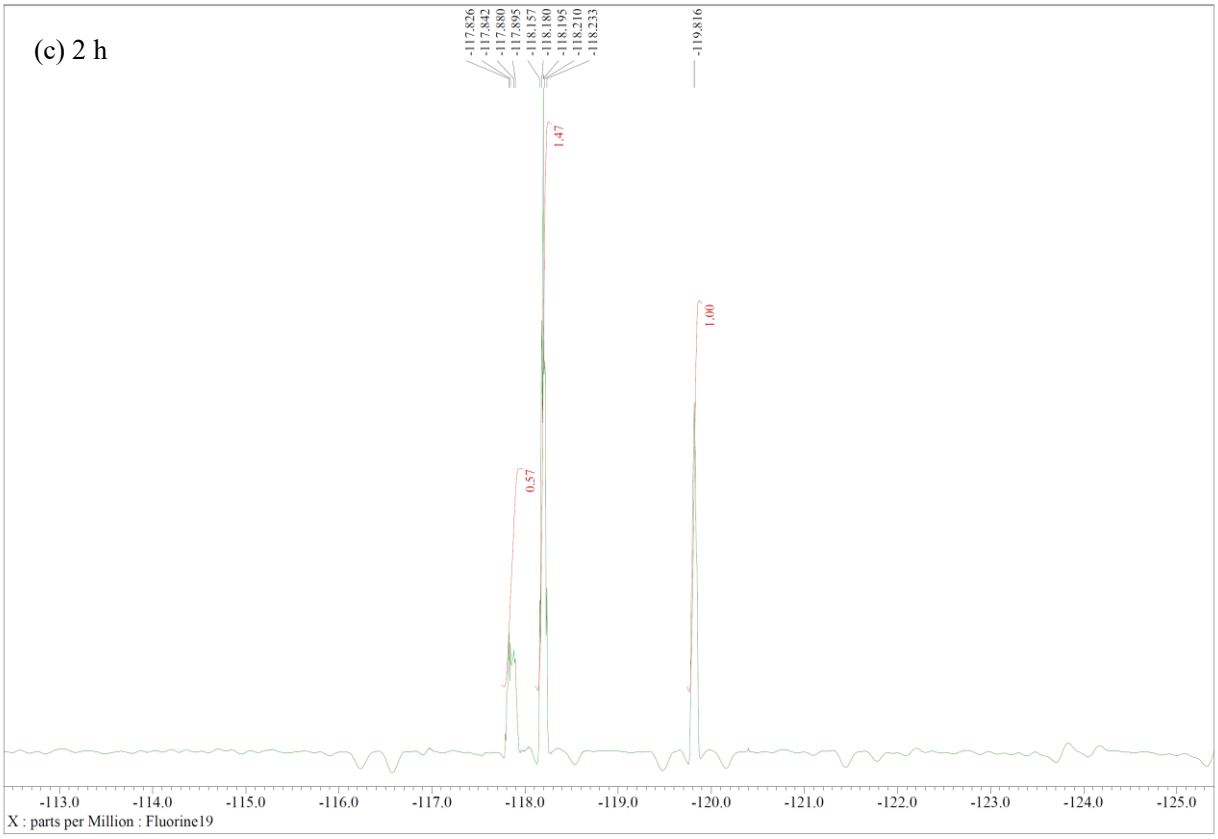
(c) 2 h
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-118.180
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-119.816
1.47
1.00
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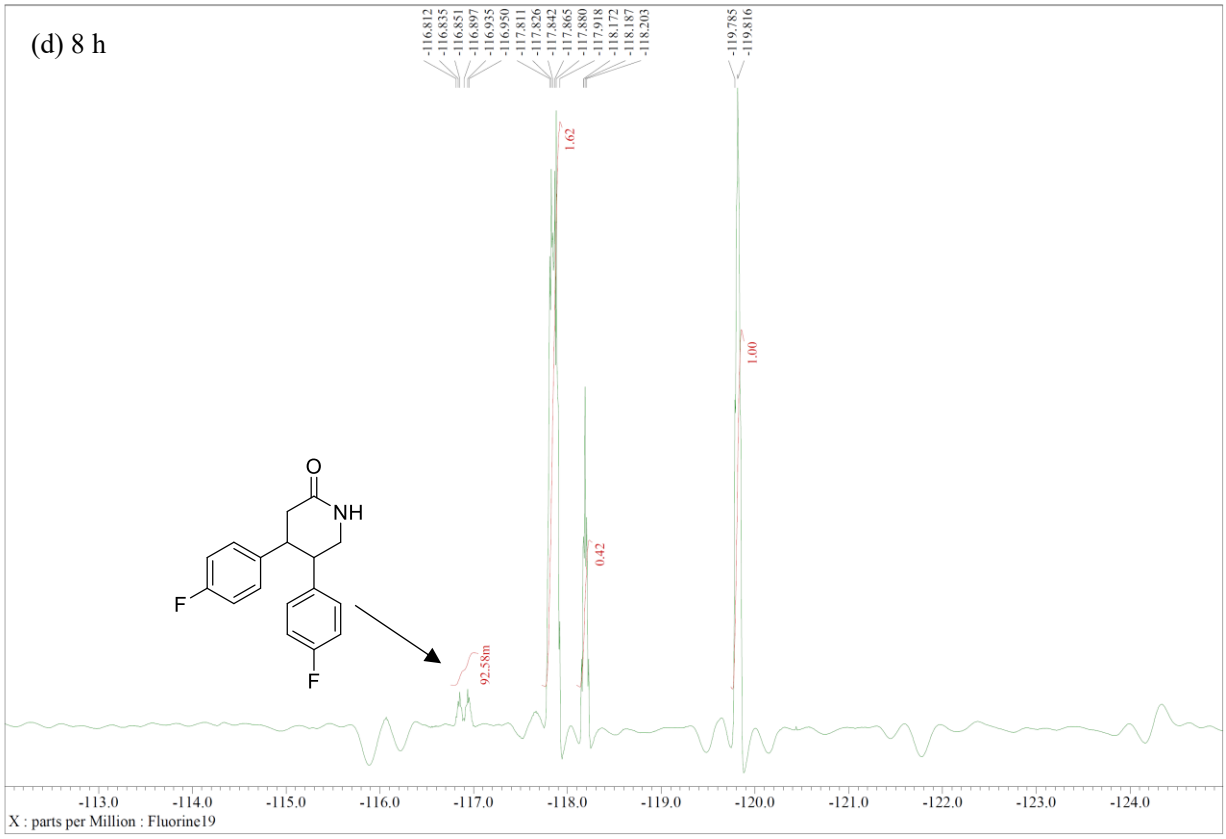


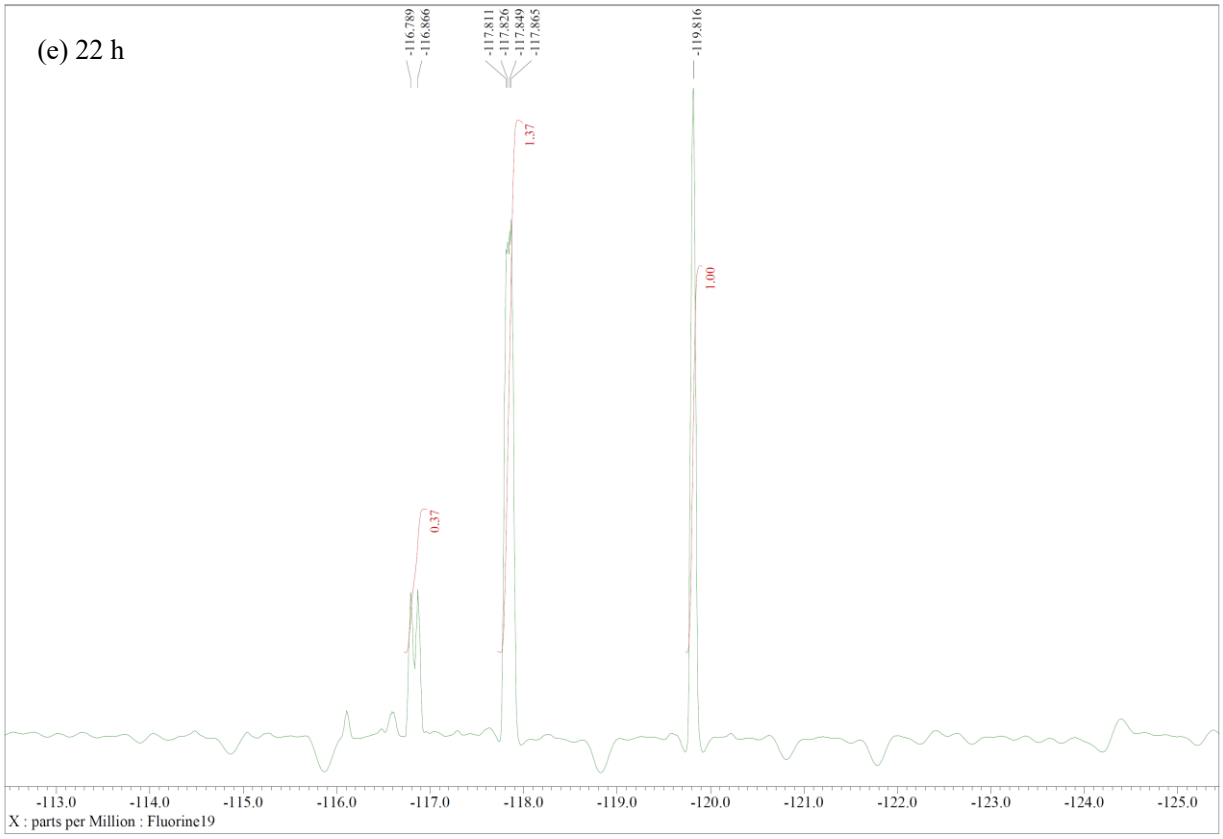


Figure S11. The reaction profile monitored by ^{19}F NMR. (a) 0 h (Before addition of TsOH). (b) 1 hour (After the reaction started). (c) 2 h. (d) 8 h. (e) 22 h.

5. References

[1] Tomiya, I.; Wu, Y.; Hyodo, K. Ring-Opening Amino Esterification of Cyclic Ketones to Access Distal Amino Acid Derivatives. *Adv. Synth. Catal. doi.org/10.1002/adsc.202301421*.

[2] Shima, Y.; Igarashi, E.; Yoshimura, T.; Matsuo, J. Reactions of Nitrosobenzenes with Cyclobutanones by Activation with a Lewis Acid. *Synlett*, **2018**, *29*, 723-726.

[3] Hyodo, K.; Togashi, K.; Oishi, N.; Hasegawa, G.; Uchida, K. Brønsted acid catalyzed nitrile synthesis from aldehydes using oximes via transoximation at ambient temperature. *Org. Lett.* **2017**, *19*, 3005-3008.

[4] Hyodo, K.; Miki, K.; Yauchi, T. Synthesis of Ethyl Acetohydroximate and Derivatives from Imidate Hydrochloride. *J. Org. Chem.* **2022**, *87*, 2959-2965.

[5] Lang, Q.; Gu, G.; Cheng, Y.; Yin, Q.; Zhang, X. Highly Enantioselective Synthesis of Chiral γ-Lactams by Rh-Catalyzed Asymmetric Hydrogenation. *ACS Catal*, **2018**, *8*, 4824-4828.

[6] Biswas, K.; Gholap. R.; Srinivas, P.; Kanyal S.; Sarma, K. D. β-Substiteted γ-butyrolactams from mucochloric acid: synthesis of (±)baclofen and other γ-aminobutyric acids and useful building blocks. *RSC. Adv*, **2014**, *4*, 2538-2545.

[7] Sudalai, A.; Paraskar, A. S. Co-catalyzed reductive cyclization of azido and cyano substituted α,β-unsaturated esters with $NaBH_4$: enantioselective synthesis of (*R*)-baclofen and (*R*)-rolipram. *Tetrahedron*, **2006**, *62*, 4907-4916.

[8] Montoya-Balbás, I. J.; Valentin-Guevara, B.; López-Mendoza, E.; Linzaga-Elizalde, I.; Ordoñez, M.; Román-Bravo, P. Efficient Synthesis of *β*-Aryl-*γ*-lactams and Their Resolution with (*S*)-Naproxen: Praparation of (*R*)- and (*S*)- Baclofen. *Molecules*, **2015**, *20*, 22028-22043.

[9] Schmidt, B.; Elizarov, N.; Berger, R.; Petersen, M. H. From Paracetamol to Rolipram and Derivatives: Application of Deacetylation–Diazotation Sequences and Palladium-Catalyzed Matsuda–Heck Reaction. *Synthesis*, **2013**, *45*, 1174-1180.

[10] S. Roller, C. Siegers and R. Haag, Dendritic polyglycerol as a high-loading support for parallel multistep synthesis of GABA lactam analogues. *Tetrahedron*, **2004**, *60*, 8711-8720.

[11] Smith, S. N.; Trujillo, C.; Connon, S. J. Catalytic, asymmetric azidations at carbonyls: achiral and *meso*-anhydride desymmetrisation affords enantioenriched *γ*-lactams. *Org. Biomol. Chem.* **2022**, *20*, 6384-6393.

[12] Liu, G.-X.; Liang, H.-C.; Fu, X.; Tang, J.; Hu, W.-H.; Qiu, H. Photoredox-Catalyzed Carbonyl Alkylative Amination with Diazo Compounds: A Three-Component Reaction for the Construction of γ-Amino Acid Derivatives. *Org. Lett.* **2022**, *24*, 4908-4913.

[13] Ong, M.; Mück-Lichtenfeld, C.; Daniliuc, C. G.; Wahl, J. M.; Desymmetrization of Prochiral Cyclobutanones via Nitrogen Insertion: A Concise Route to Chiral γ-Lactams. *Angew. Chem. Int. Ed.* **2021**, *60*, 9719-9723.

[14] Moriyama, K.; Ishida, K.; Togo, H. Effect of catalytic alkali metal bromide on Hofmann-type rearrangement of imides. *Chem. Commun.* **2012**, *48*, 8574-8576.

[15] Mourelle-Insua, Á.; Zampieri L. A.; Lavandera, I.; Gotor-Fernández, V. Conversion of γ- and δ-Keto Esters into Optically Active Lactams. Transaminases in Cascade Processes. *Adv. Synth. Catal.* **2018**, *360*, 686-695.

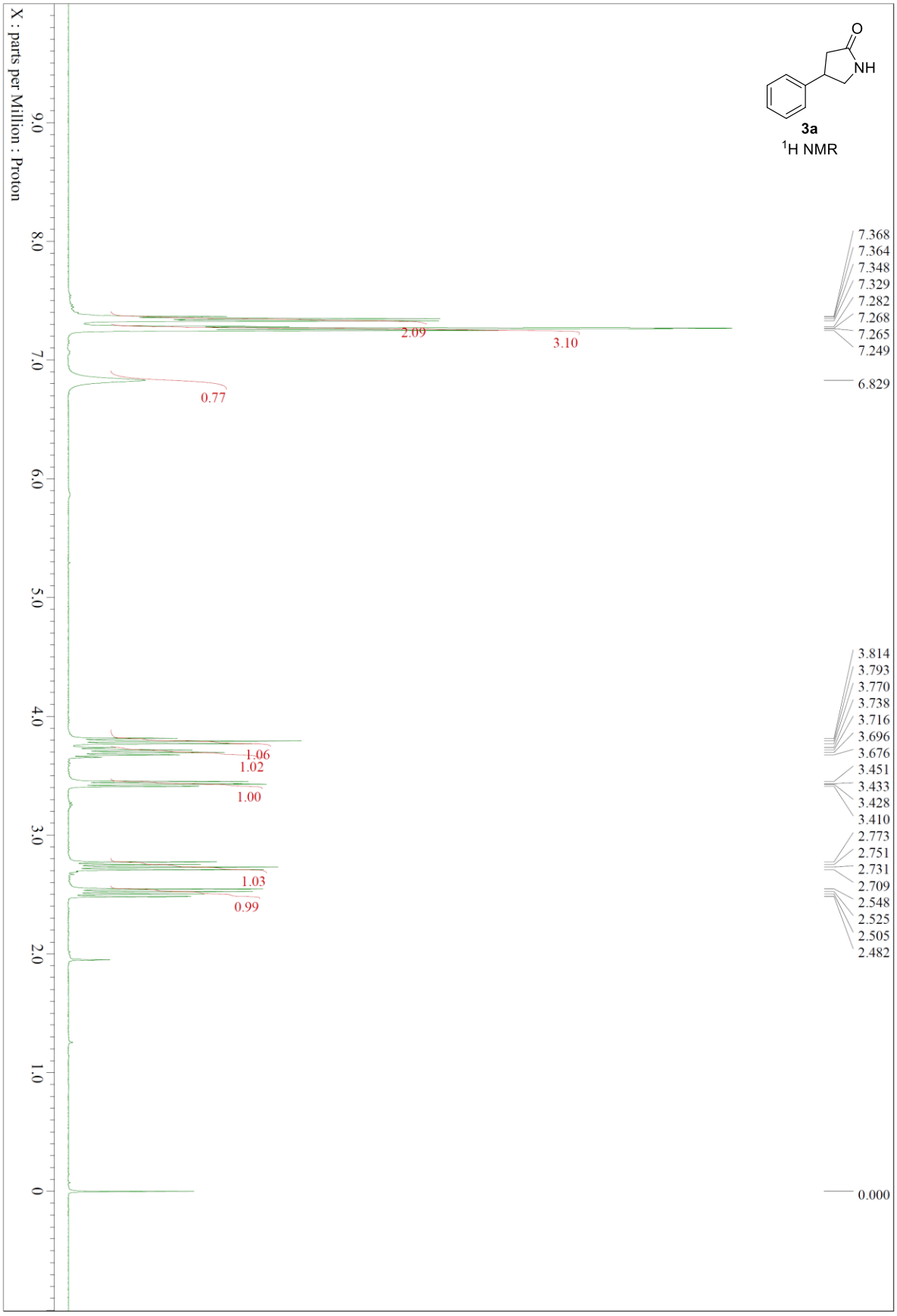
[16] Shi, Y.; Tan, X.; Gao, S.; Zhang, Y.; Wang, J. Zhang, X.; Yin, Q. Direct Synthesis of Chiral NH lactams via Ru-Catalyzed Asymmetric Reductive Amination/Cyclization Cascade of Keto Acids/Esters. *Org. Lett.* **2020**, *22*, 2707-2713.

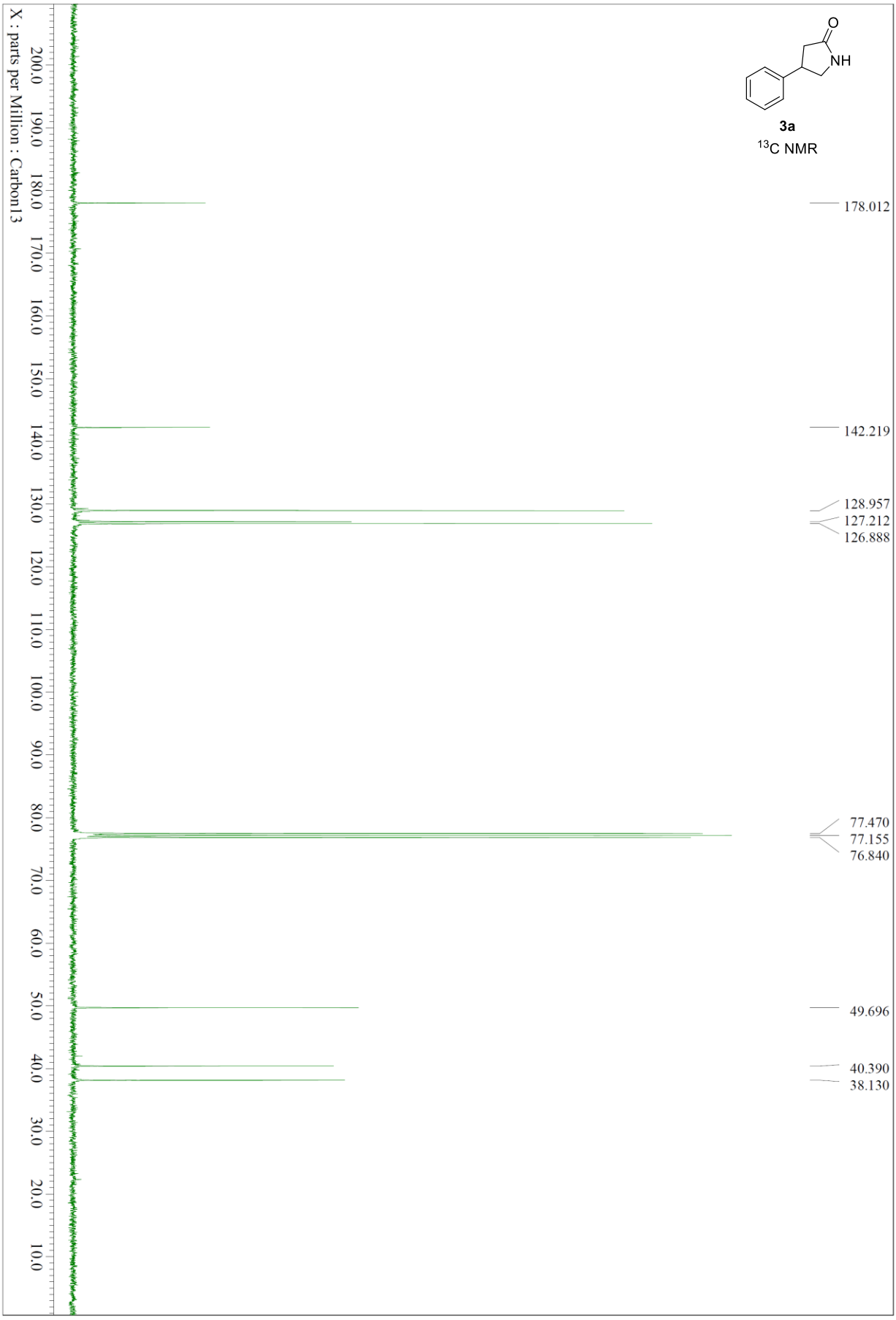
[17] Rosenmund, K. W.; Zymalkowski, F.; Engels, P. Über die Synthese von γ-Oxyphenyl- und γ- Dioxphenyl-butyrolactonen. *Chem. Eur. J.* **1951**, *84*, 711-718.

[18] Wang, H.; Park, Y. Bai, Z. Chang, S.; He, G.; Chen, G. Iridium-Catalyzed Enantioselective C(sp^3)-H Amidation Controlled by Attractive Noncovalent Interactions. *J. Am. Chem. Soc.* **2019**, *141*, 7194-7201.

[19] Zhou, Z.; Chen, S.; Hong, Y.; Winterling, E.; Tan, Y.; Hemming, M.; Harms, K.; Houk, K. N.; Meggers, E. Non-C_2-Symmetric Chiral-at-Ruthenium Catalyst for Highly Efficient Enantioselective Intramolecular C(sp_3)-H Amidation. *J. Am. Chem. Soc.* **2019,** *141*, 19048-19057.
[20] Rigo, B.; Fasseur, D.; Cherepy, N.; Couturier, D. Decarboxylation of pyroglutamic acids with P2O5/CH3SO3H : A general synthesis of 5-aryl-2-pyrrolidinones. *Tetrahedron. Lett.* **1989**, *30*, 7057-7060.
[21] Liu, J.; Ye, W.; Wang, S.; Zheng, J.; Tang, W.; Li, X. Synthesis of Lactams via Ir-Catalyzed C-H Amidation Involving Ir-Nitrene Intermediates. *J. Org. Chem.* **2020**, *85*, 4430-4440.
[22] Armanio, N.; Carreira, E. M. Ruthenium-Catalyzed Intramolecular Hydrocarbamoylation of Allylic Formamides: Convenient Access to Chiral Pyrrolidones. *J. Am. Chem. Soc.* **2013**, *135*, 6814-6817.
[23] Miller, R. D.; Goelitz, P. An efficient and general synthesis of 5-substituted pyrrolidinones. *J. Org. Chem*. **1981**, *46*, 1616-1618.
[24] Keum, H.; Jung, H.; Jeong, J.; Kim, D. Chang, S. Visible-Light Induced C(sp^2)-H Amidation with an Aryl-Aryl *σ*-Bond Relocation via Redox-Neutral Radical-Polar Crossover. *Angew. Chem. Int. Ed.* **2021**, *60*, 25235-25240.
[25] Hwang, Y.; Jung, H.; Lee, E.; Kim, D.; Chang, S. Quantitative Analysis on Two-Point Ligand Modulation of Iridium Catalysts for Chemodivergent C-H Amidation. *J. Am. Chem. Soc.* **2020**, *142*, 8880-8889.
[26] Langlois, N.; Wang, H.-S. Synthesis of the Novel Antidepressant (R)-(-)-Rolipram. *Synth. Commun.* **1997**, *27*, 3133–3144.
[27] Crudden, C. M.; Ziebenhaus C.; Rygus, J. P. G.; Ghozati, K.; Unsworth P. J.; Nambo, M.; Voth, S.; Hutchinson, M.; Laberge, V. S.; Maekawa, Y.; Imao, D. Iterative protecting group-free cross-coupling leading to chiral multiply arylated structures. *Nat. Commun.* **2016**, *7*, 11065-11071.
[28] Wang, P. Z.; He, B. Q.; Cheng, Y.; Chen. J. R.; Xiao, W. J. Radical C–C Bond Cleavage/Addition Cascade of Benzyl Cycloketone Oxime Ethers Enabled by Photogenerated Cyclic Iminyl Radicals. *Org. Lett.* **2019**, *21*, 6924-6929.
[29] Ong, M.; Arnold, M.; Walz, W. A.; Wahl, M. J. Stereospecifiv Nitrogen Insertion Using Amino Diphenylphophinates: An Aza-Baeyer-Villiger Rearrangment. *Org. Lett.* **2022**, *24*, 6171-6175.
[30] Helling, C.; Wölper, C.; Cutsail III, G. E.; Haberhauer, G. CoverFeature: A Mechanistiv Study on Reactions of Group 13 Diyls LM with Cp*SbX_2: From Stibanyl Radicals to Antimony Hydrides. *Chem. Eur. J.* **2020**, *26*, 13318-13382.
[31] Wang, P.-L.; Li, Y.; Wu, Y.; Li, C.; Lan, Q.; Wang, X.-S. Pd-Catalyzed C(sp3)−H Carbonylation of Alkylamines: A Powerful Route to γ-Lactams and γ-Amino Acids. *Org. Lett*. **2015**, *17*, 3698–3701.
[32] Biswas, K.; Gholap, R.; Srinivas, P.; Kanyal, S.; Sarma, K. β-Substituted γ-butyrolactams from mucochloric acid: synthesis of (±)-baclofen and other γ-aminobutyric acids and useful building blocks. *RSC Adv*. **2014**, *4*, 2538-2545.
[33] Ishitani, H.; Kanai, K.; Saito, Y.; Tsubogo, T.; Kobayashi, S. Synthesis of (±)-Pregabalin by Utilizing a Three-Step Sequential-Flow System with Heterogeneous Catalysts. *Eur. J. Org. Chem*, **2017**, 6491-6494.
[34] Kang, Q.-K.; Wang, L.; Liu, Q.-J.; Li, J.-F.; Tang, Y. Asymmetric H_2O-Nucleophilic Ring Opening of D–A Cyclopropanes: Catalyst Serves as a Source of Water. *J. Am. Chem. Soc.* **2015**, *137*, 14594-14597.

6. NMR spectra

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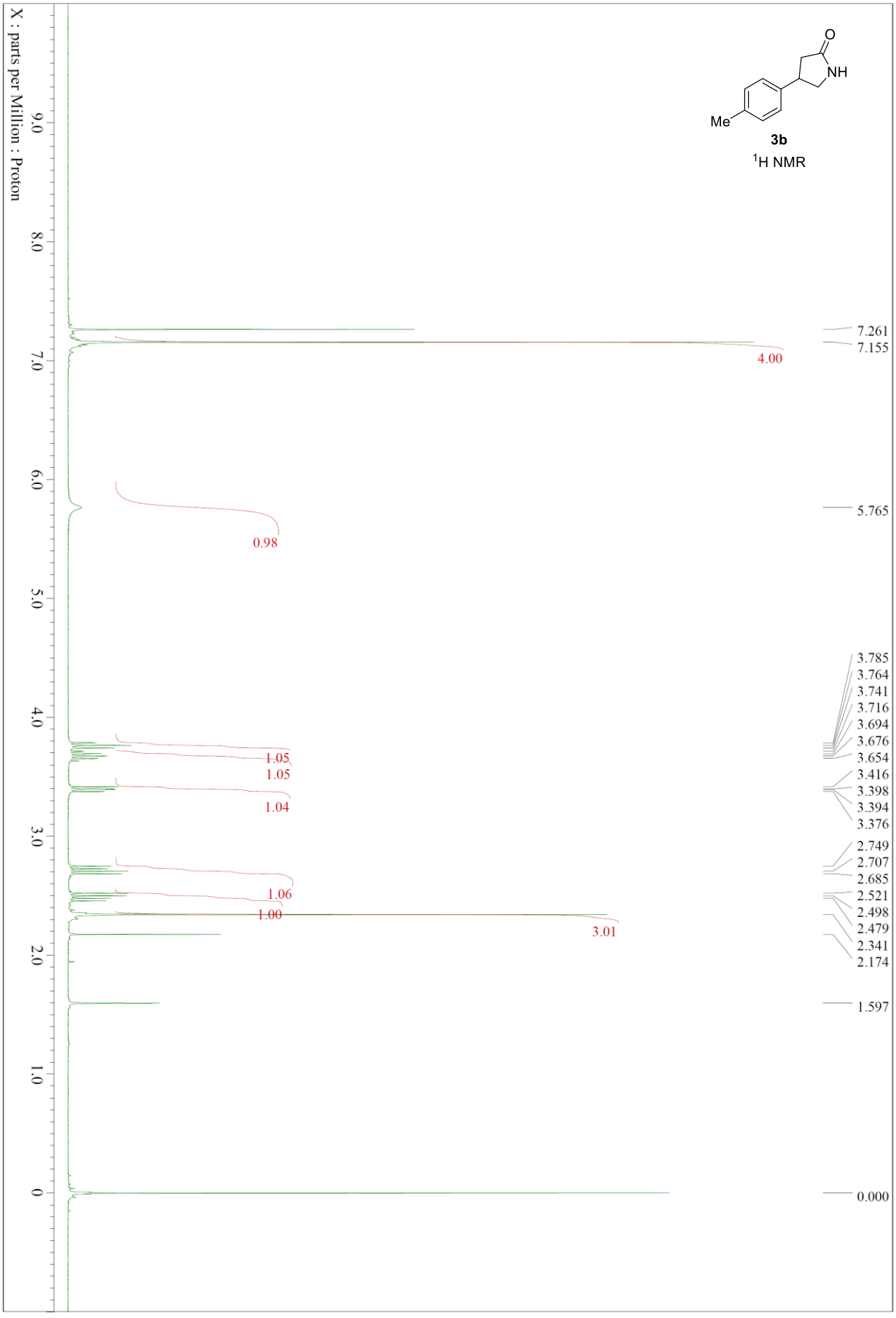
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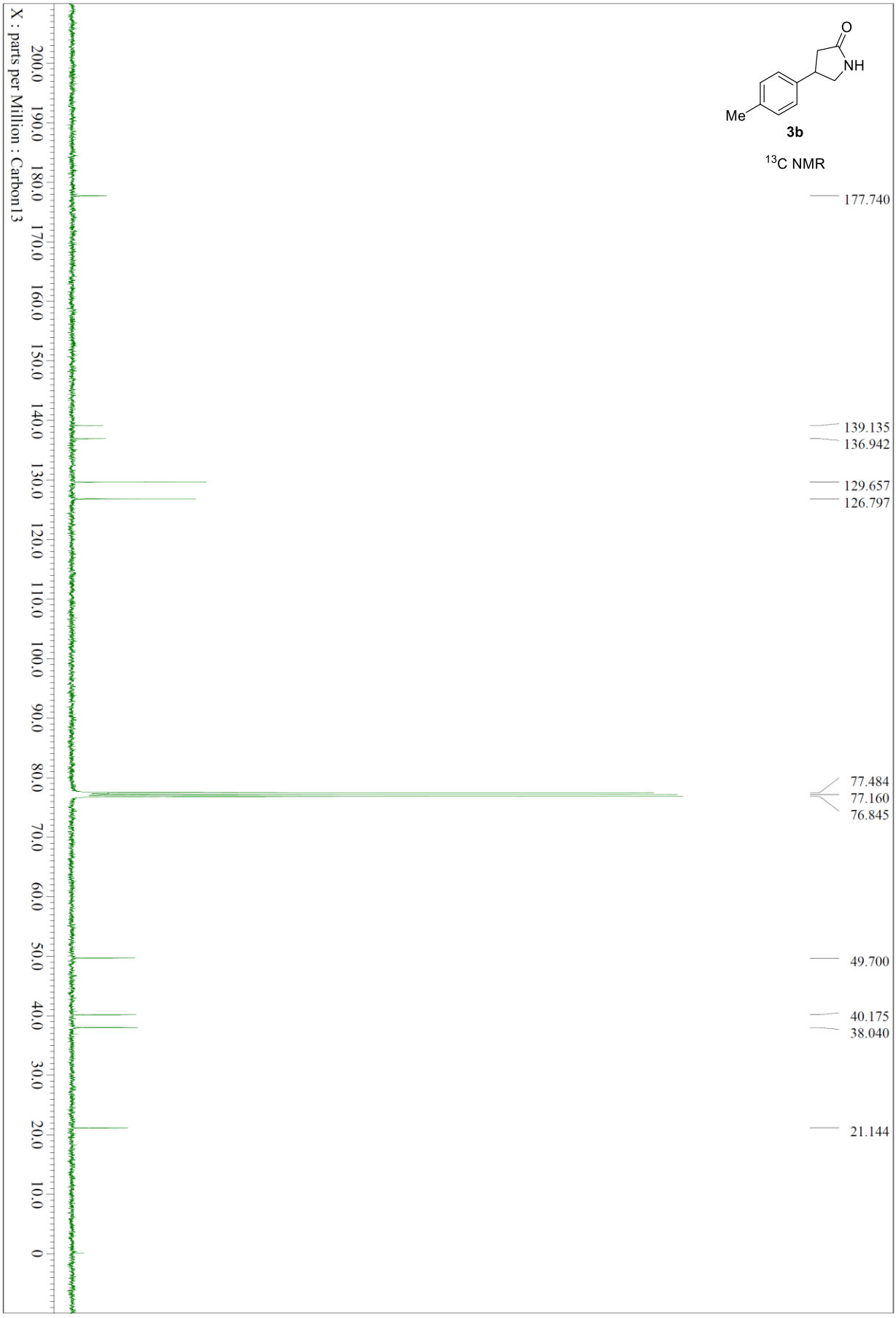
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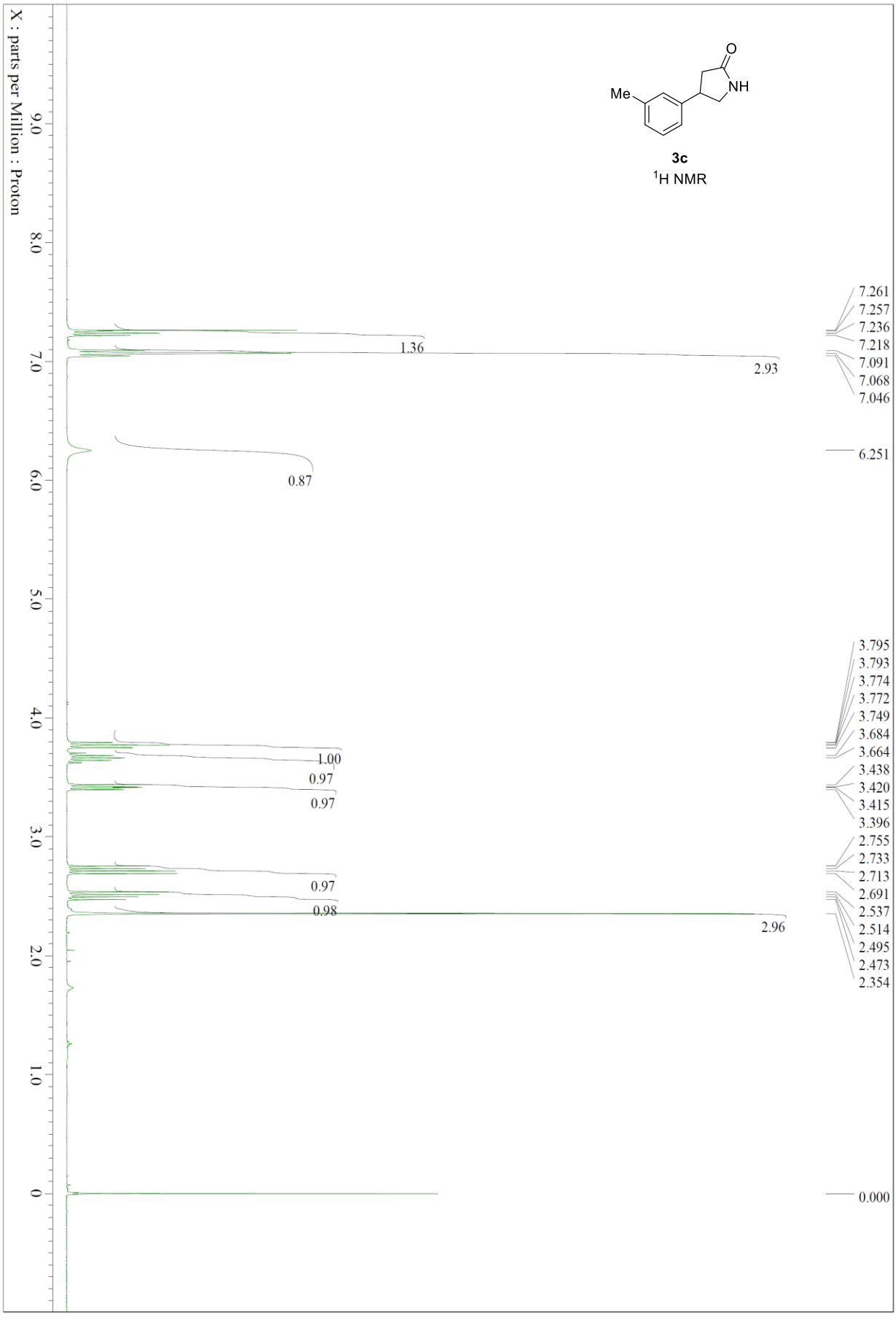
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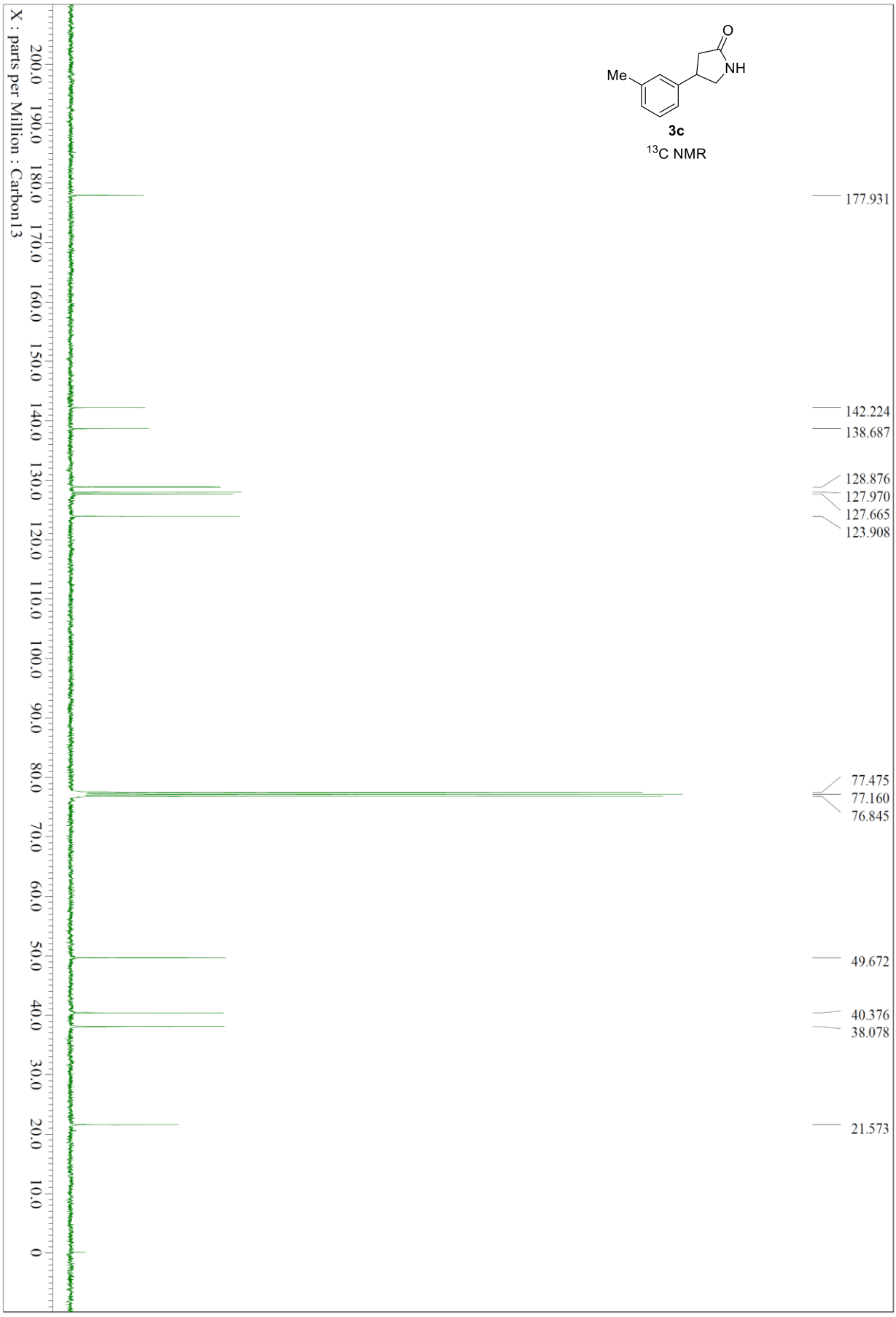
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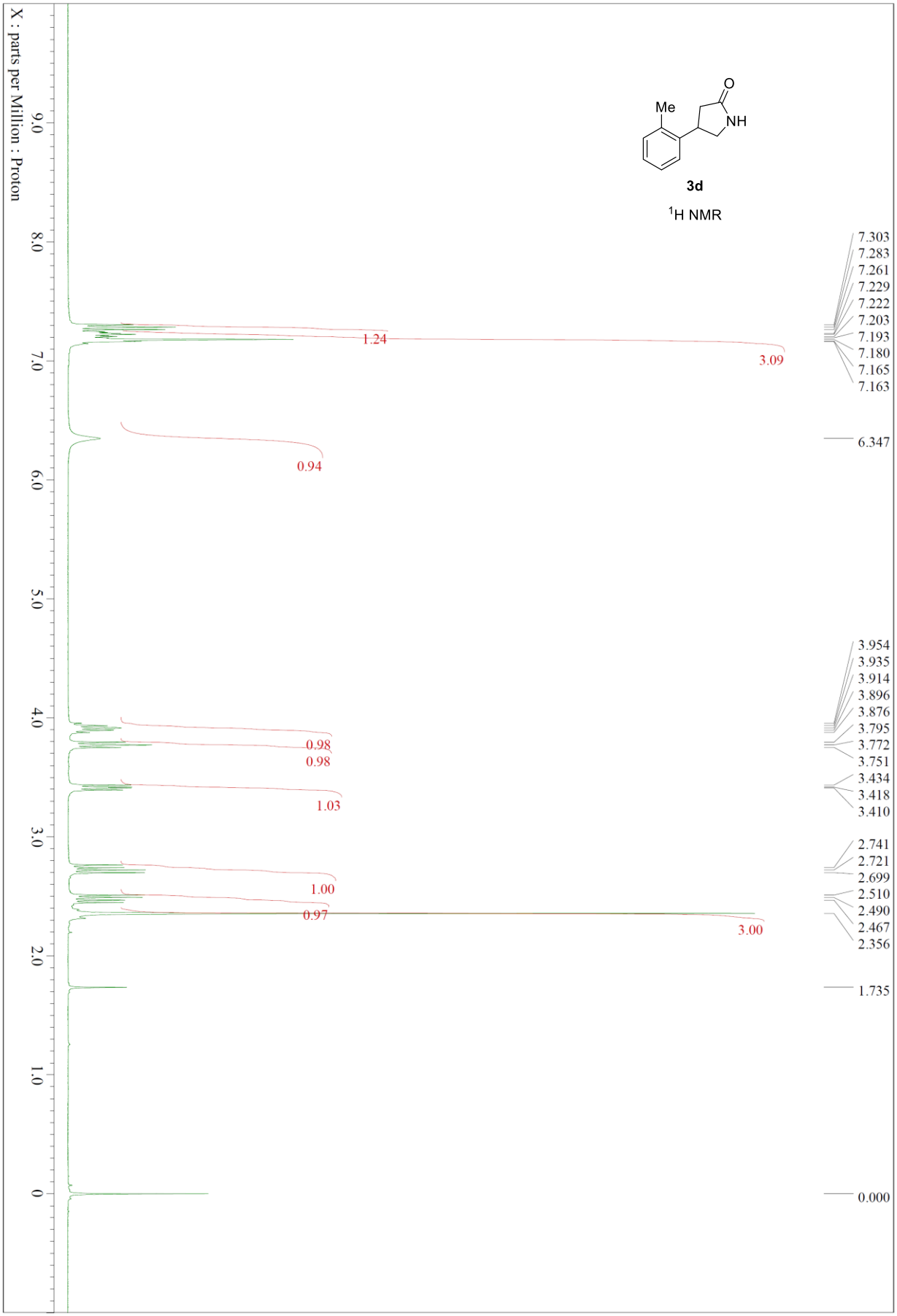
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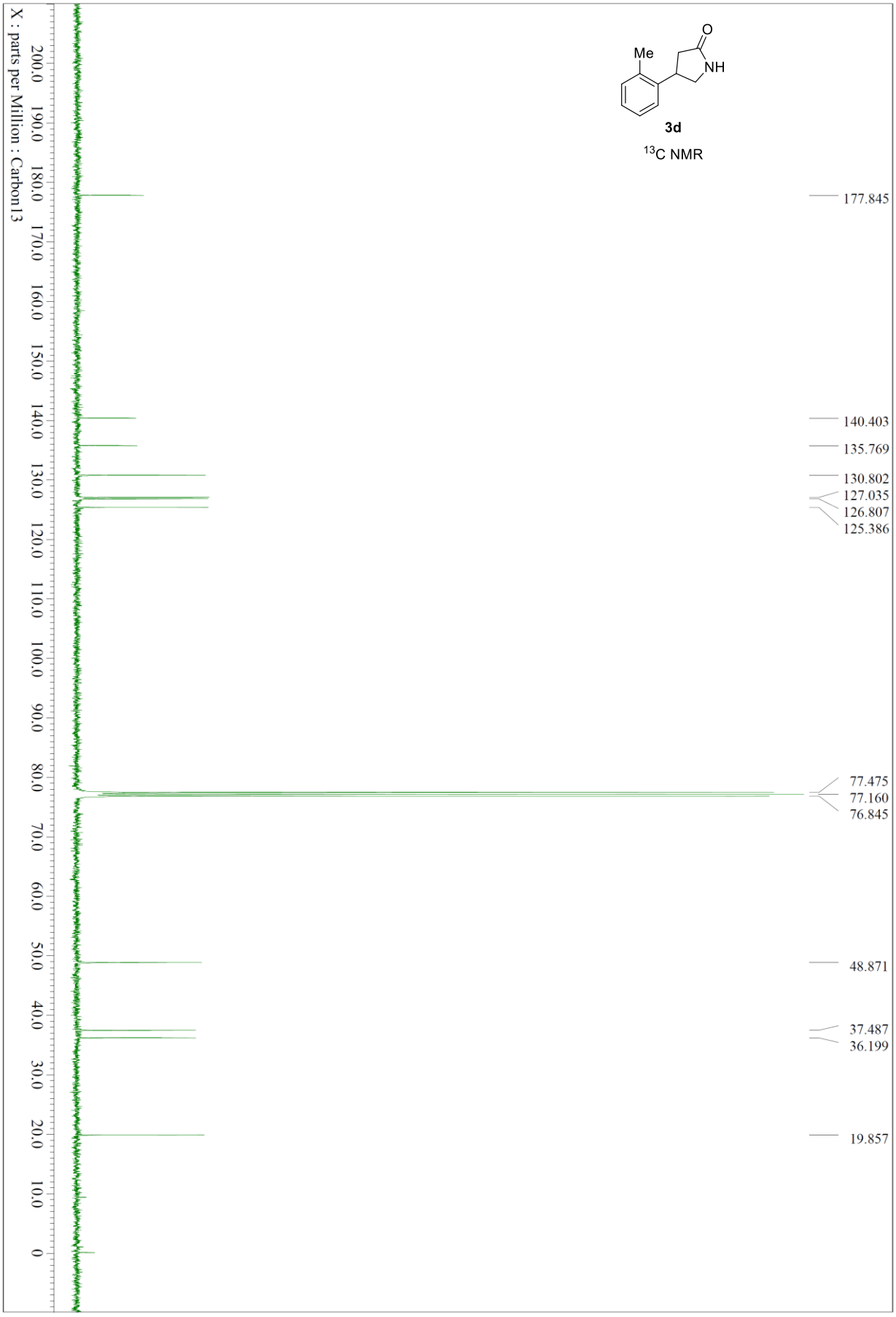
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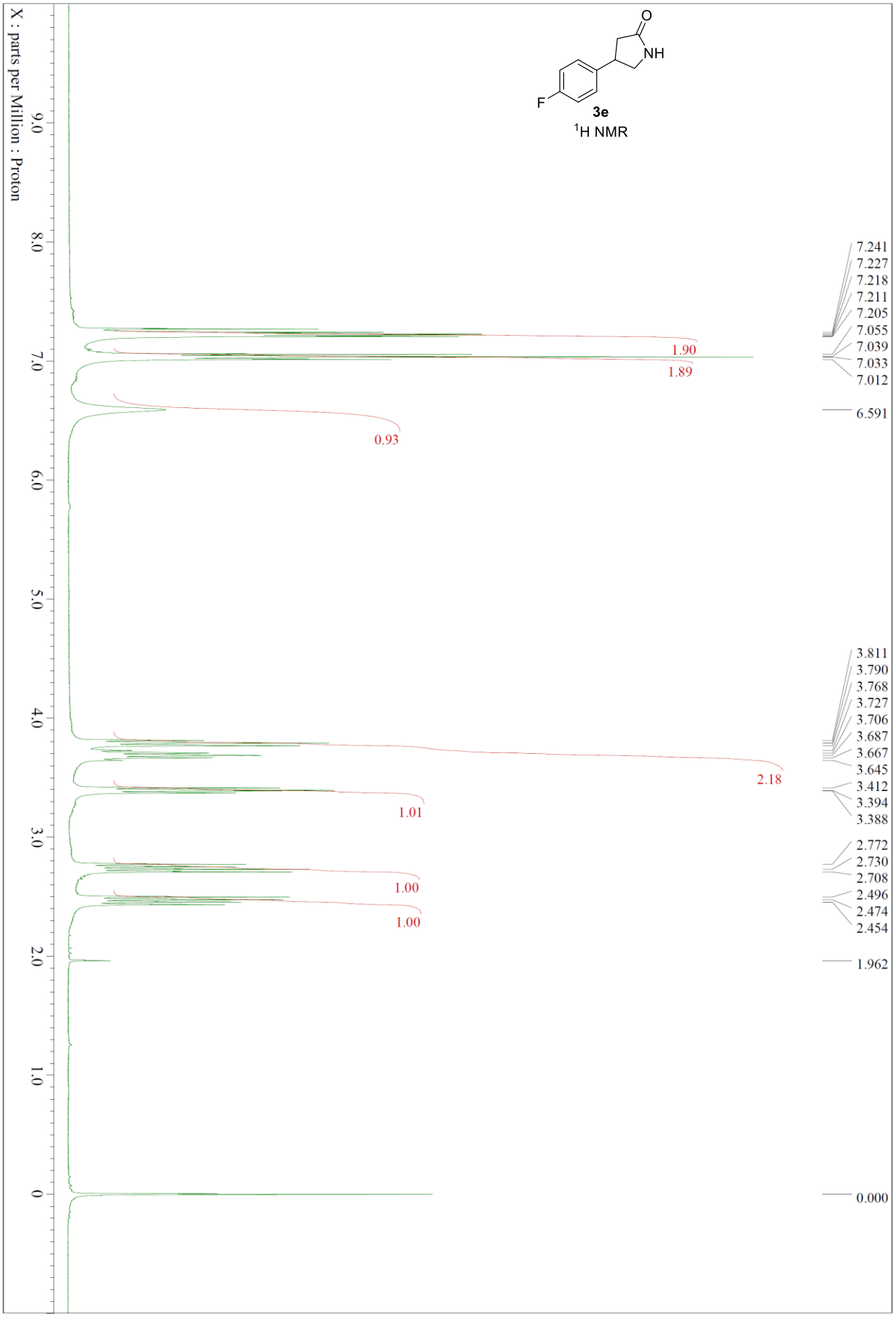
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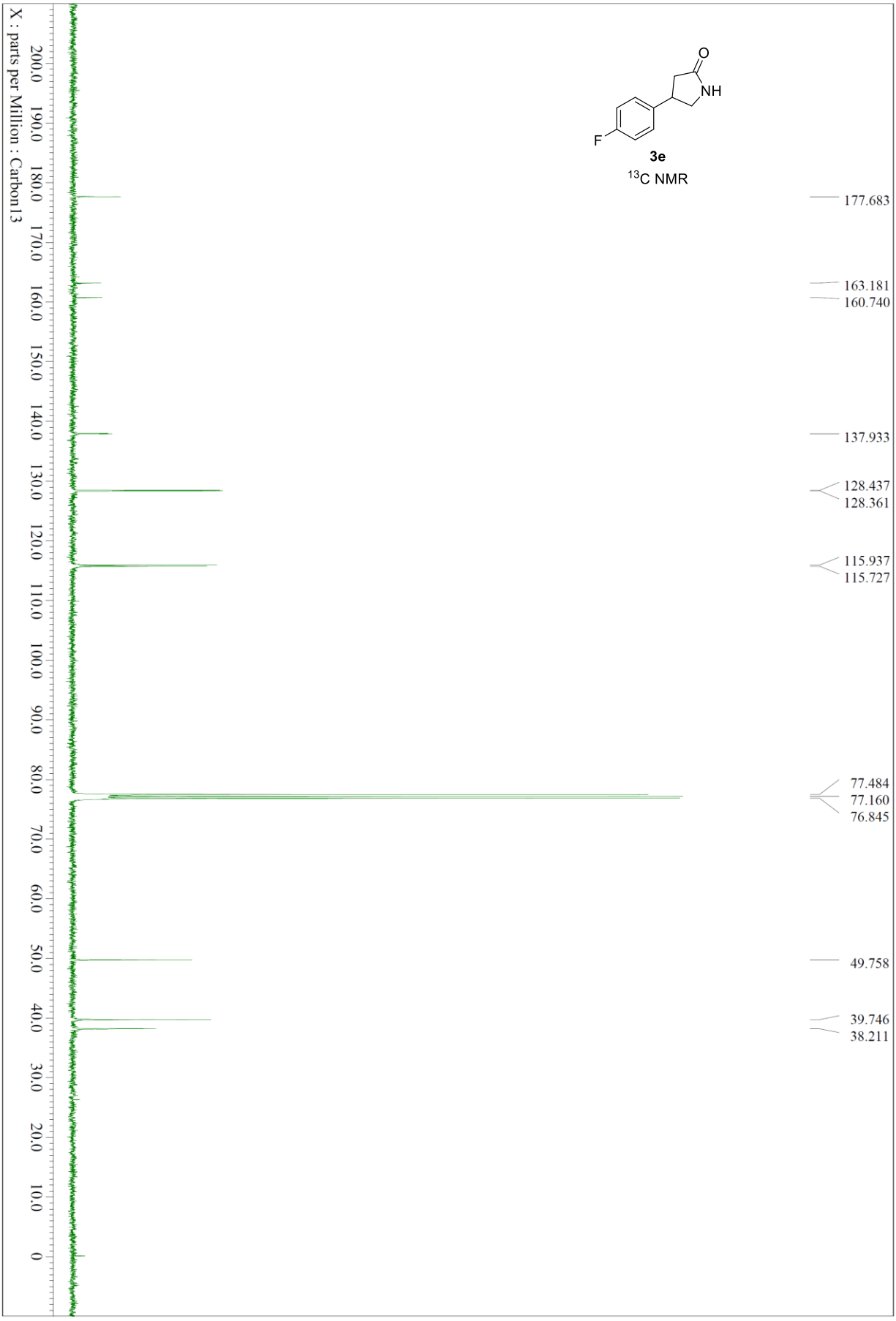
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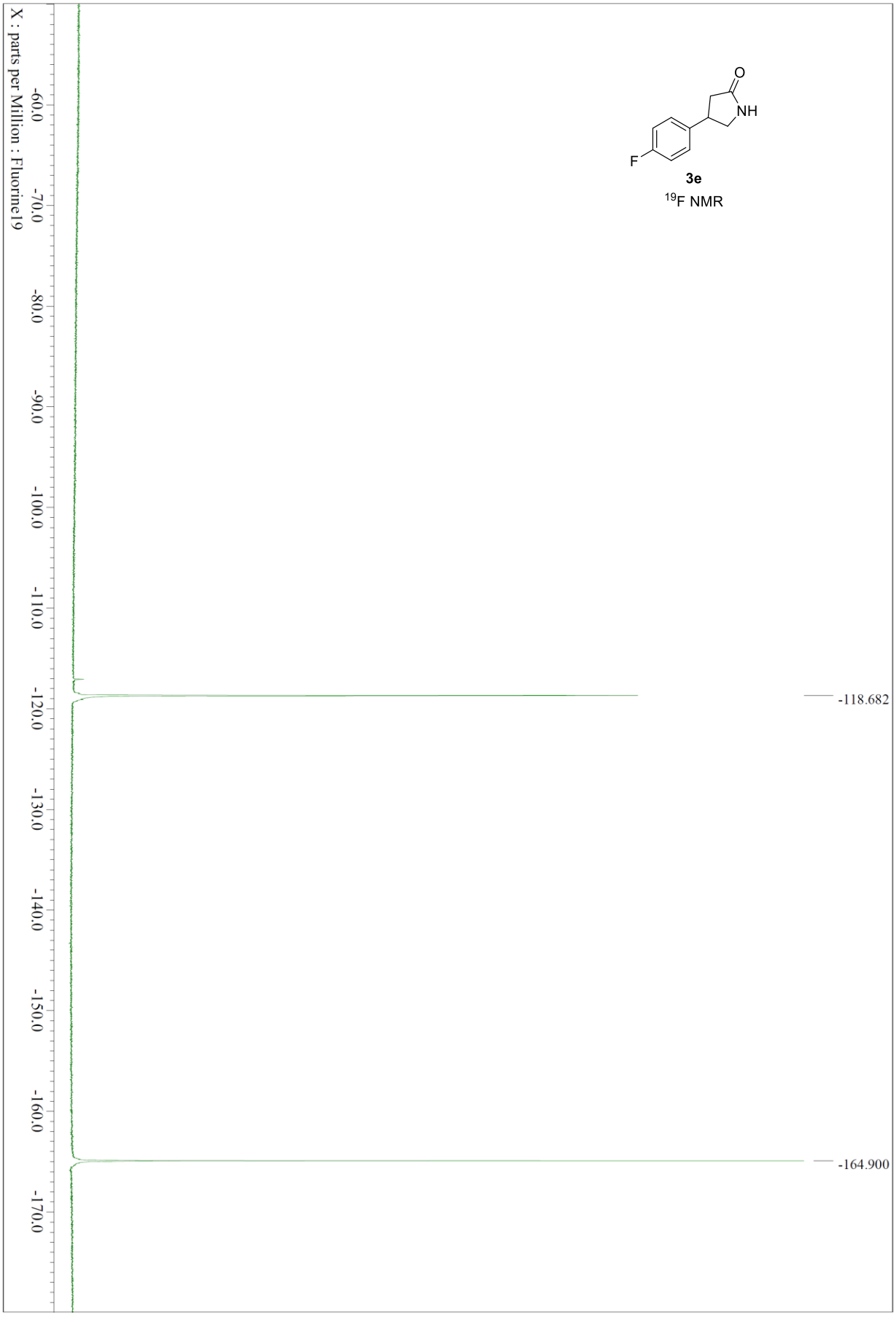
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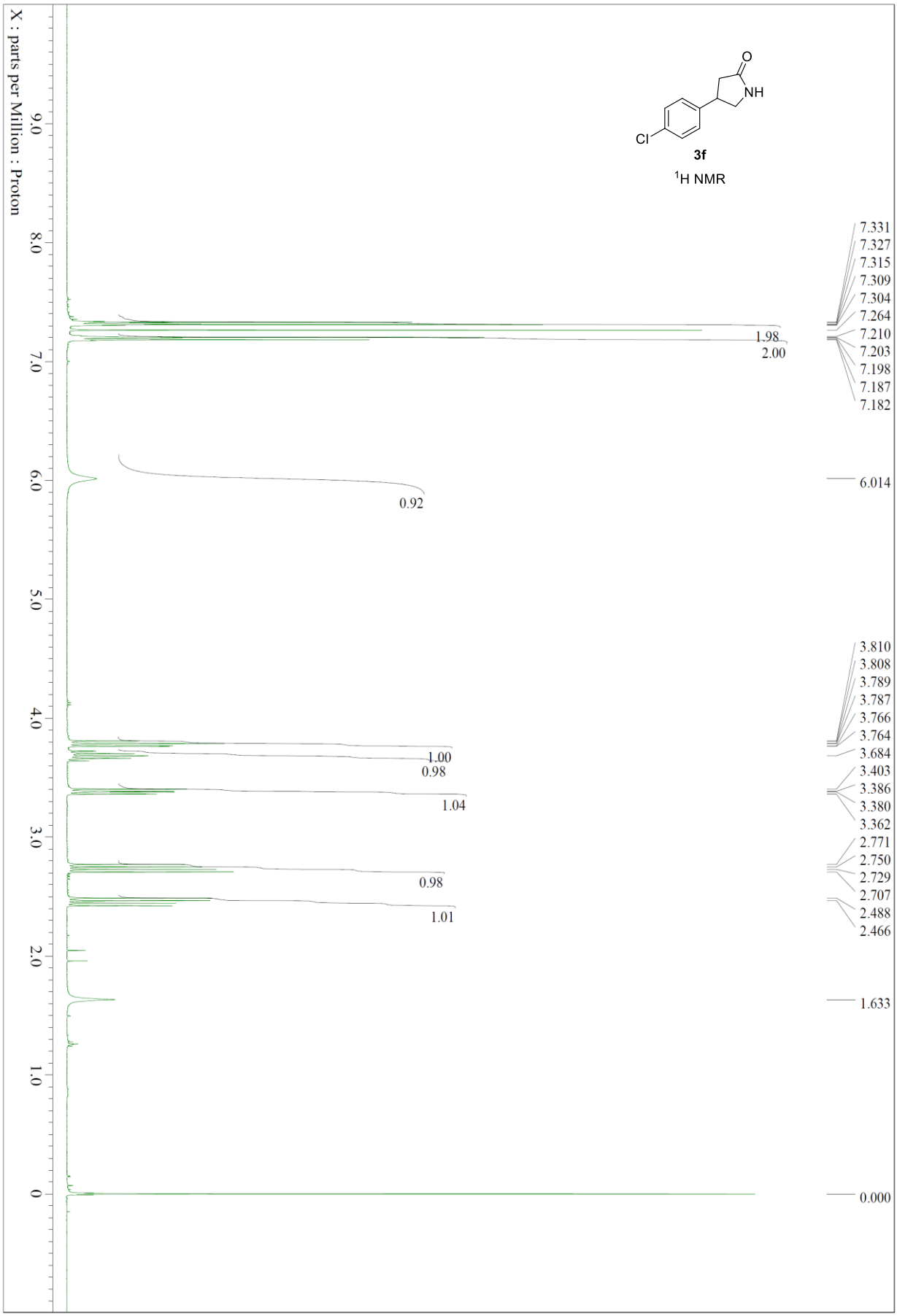
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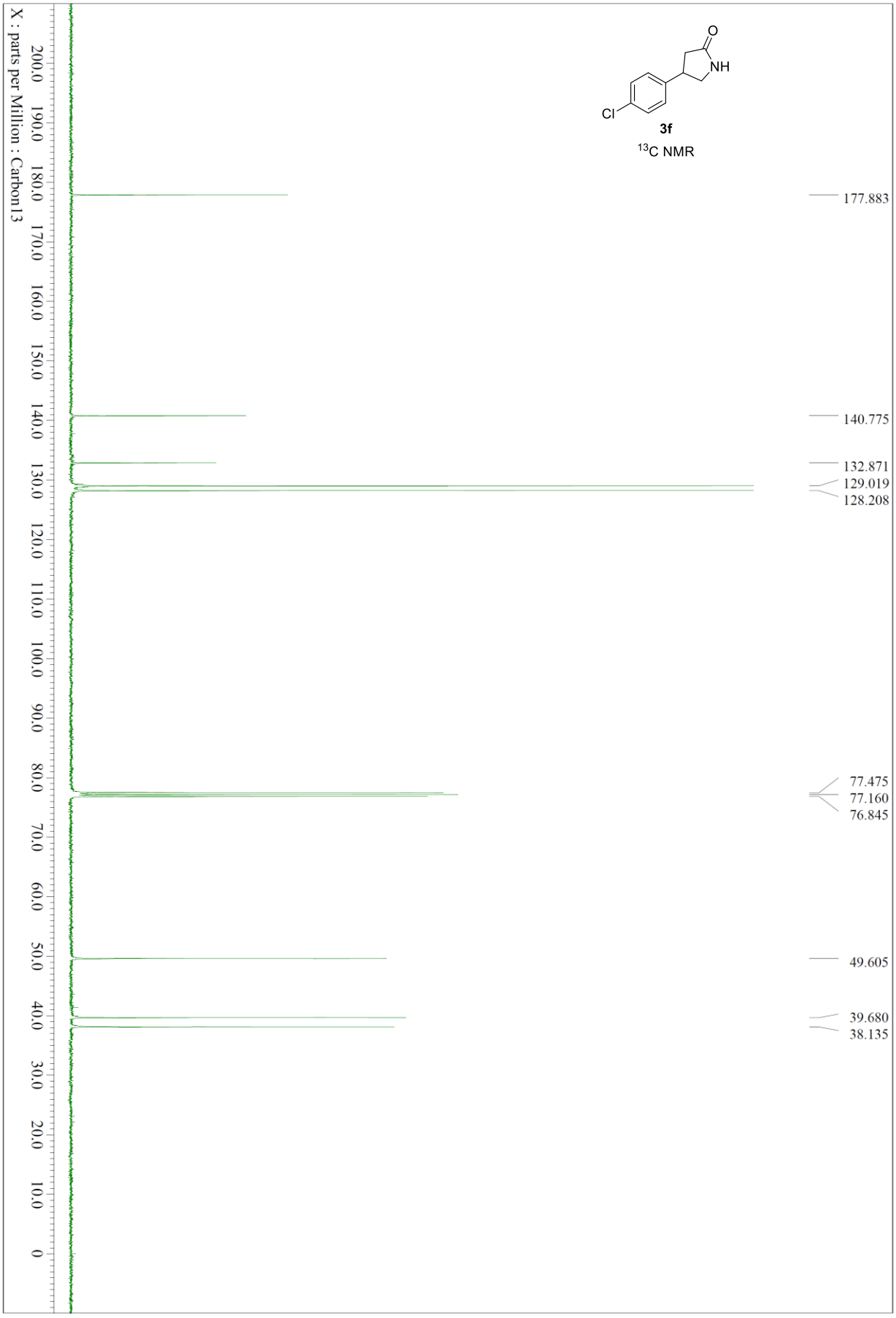
3.764
3.684
3.403
3.386
3.380
3.362
1.00
0.98
1.04
2.771
2.750
2.729
2.707
2.488
2.466
0.98
1.01
1.633
0.000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NH
Cl
3f
13C NMR
X : parts per Million : Carbon13
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190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
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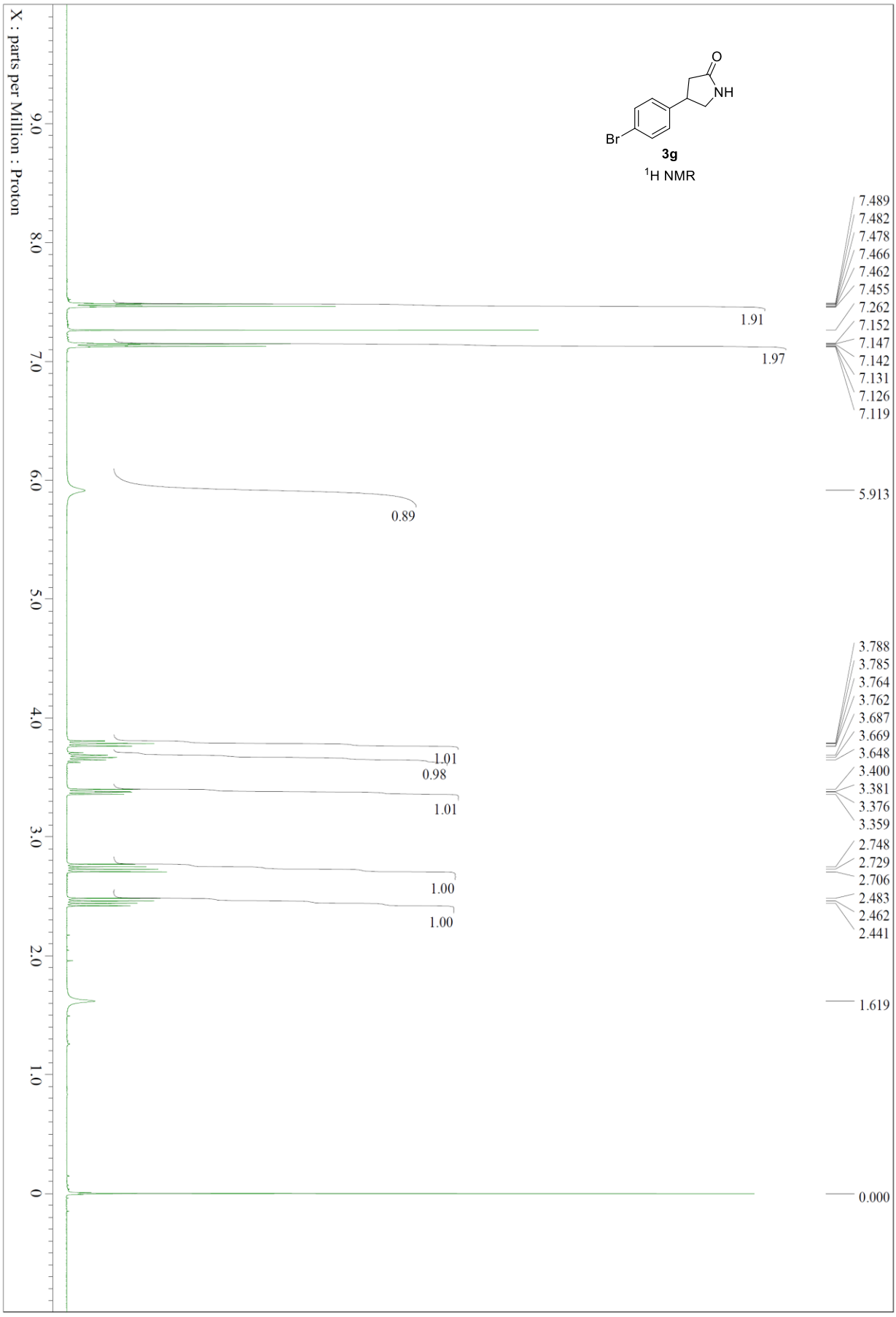
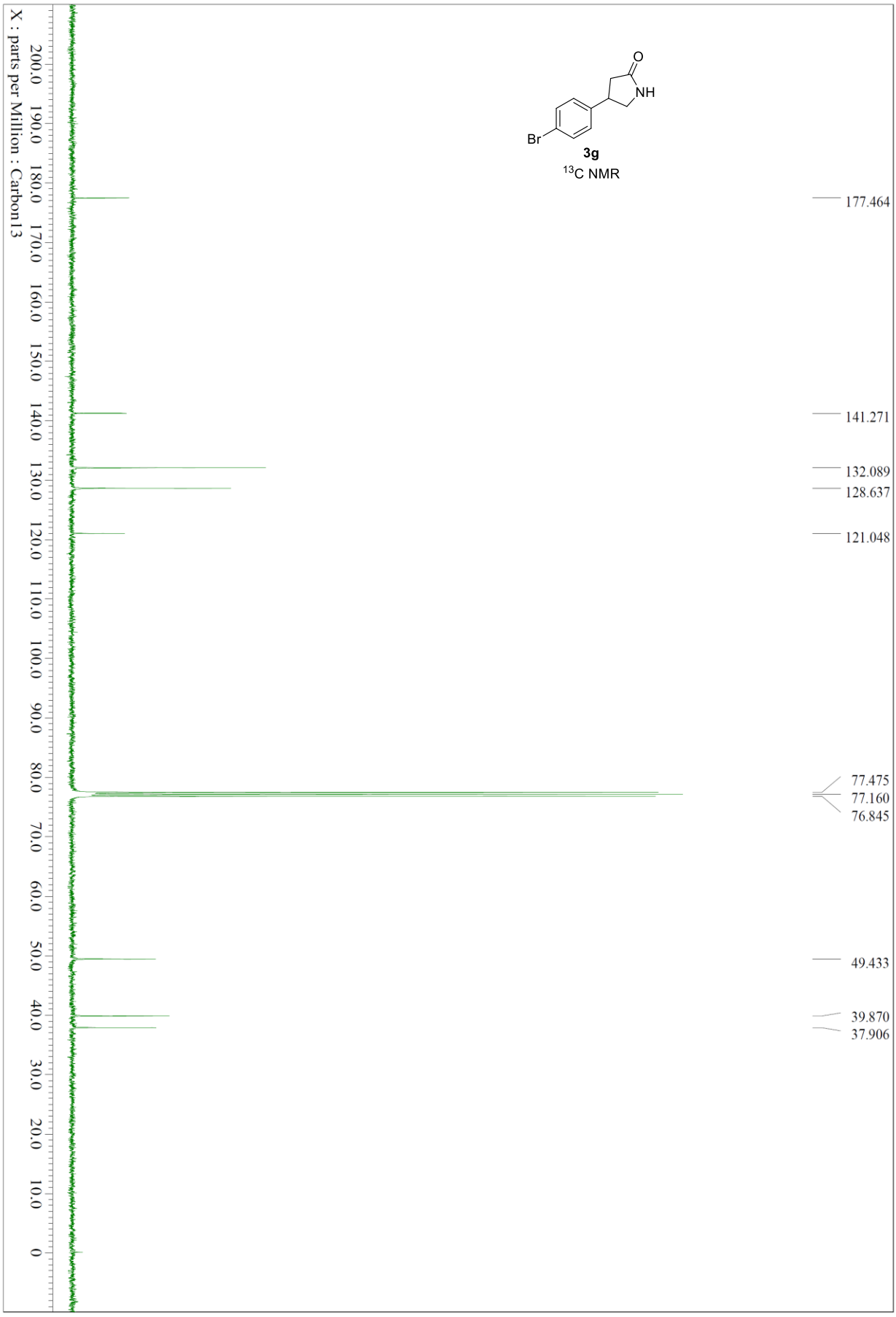
132.871
129.019
128.208
77.475
77.160
76.845
49.605
39.680
38.135


X : parts per Million : Proton
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
O
NH
Br
3g
1H NMR
7.489
7.482
7.478
7.466
7.462
7.455
7.262
7.152
7.147
7.142
7.131
7.126
7.119
5.913
3.788
3.785
3.764
3.762
3.687
3.669
3.648
3.400
3.381
3.376
3.359
2.748
2.729
2.706
2.483
2.462
2.441
1.619
0.000
1.91
1.97
0.89
1.01
0.98
1.01
1.00
1.00


O
NH
Br
3g
13C NMR
X : parts per Million : Carbon13
200.0
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
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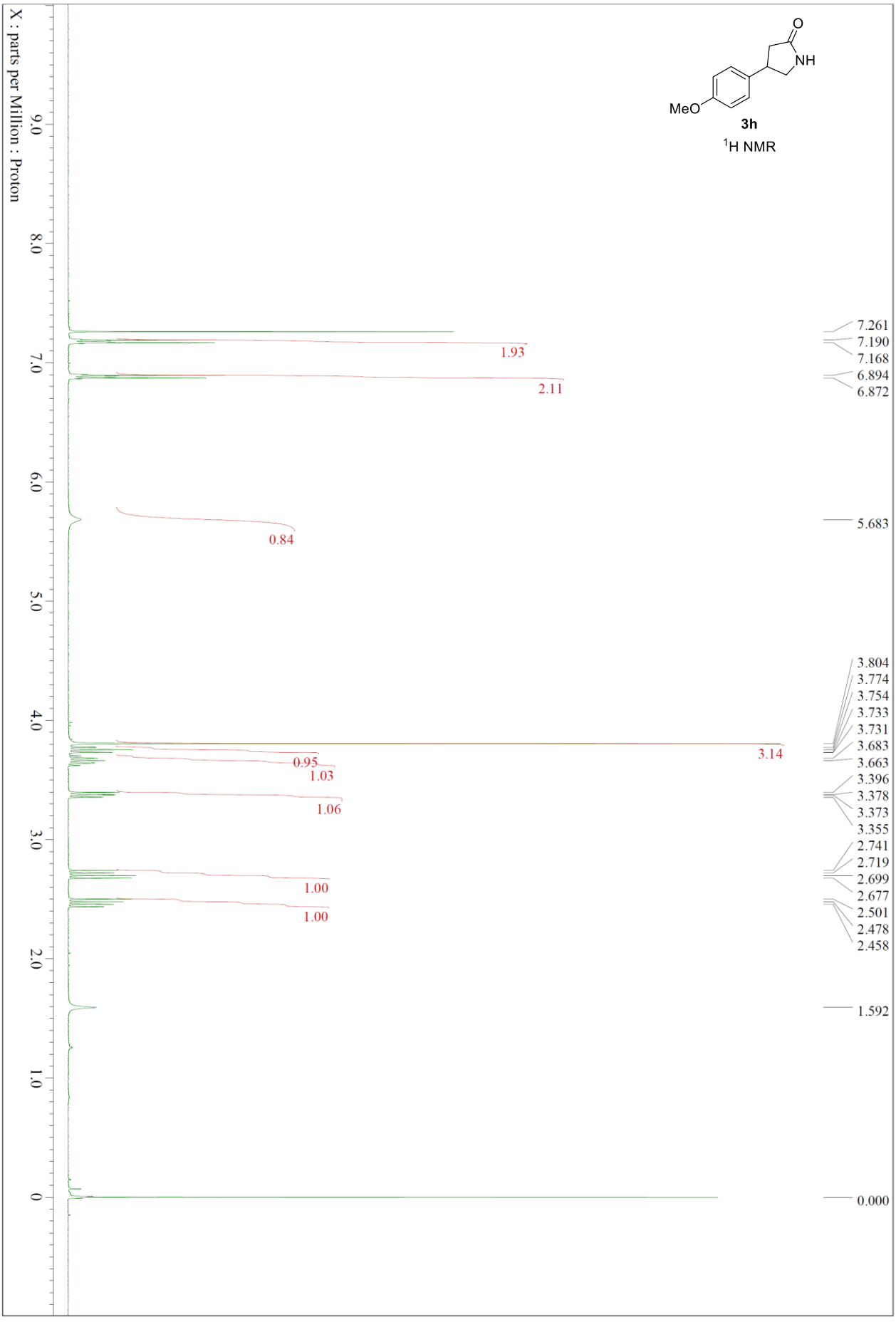
141.271
132.089
128.637
121.048
77.475
77.160
76.845
49.433
39.870
37.906


X : parts per Million : Proton
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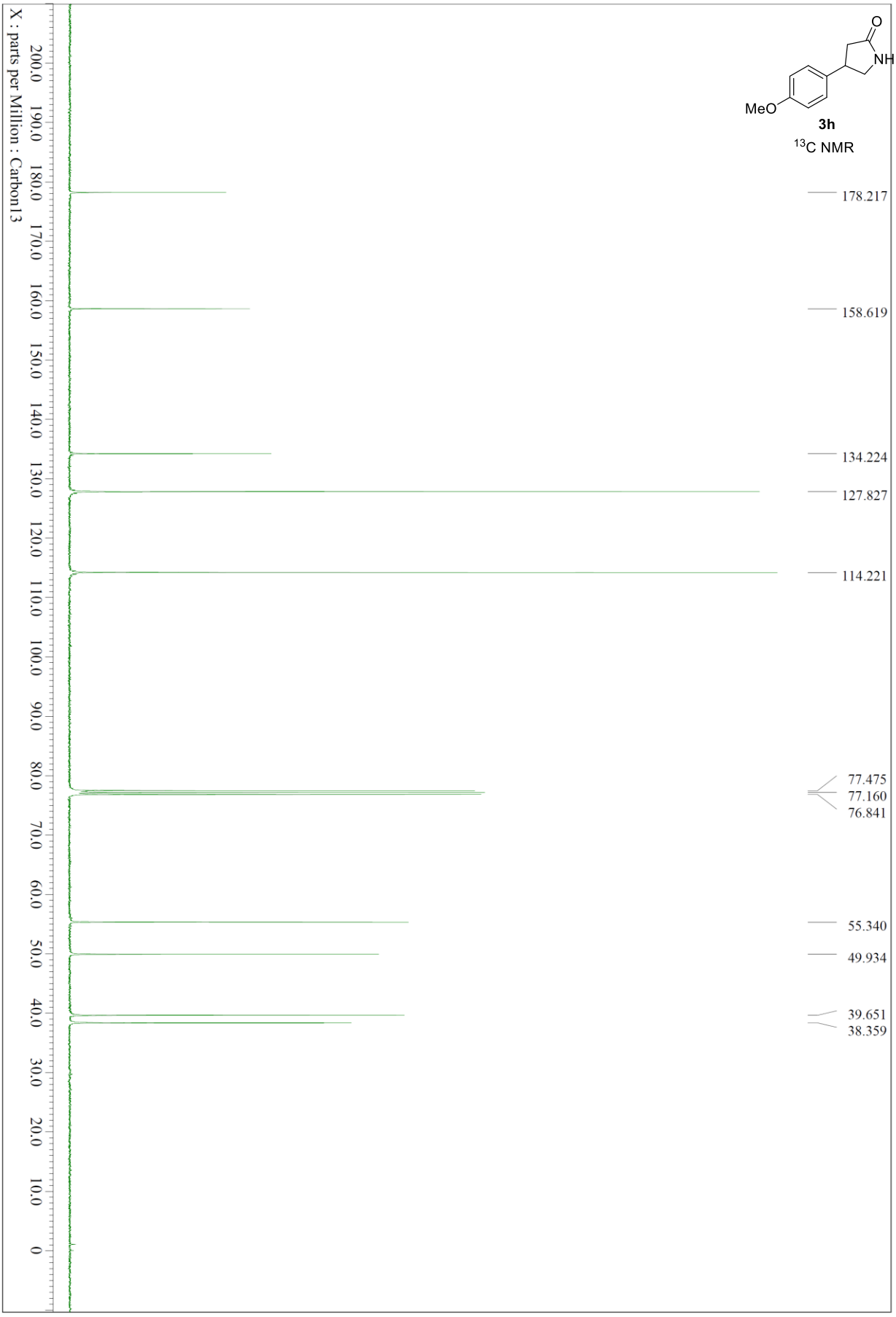
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
O
NH
MeO
3h
1H NMR
7.261
7.190
7.168
6.894
6.872
5.683
3.804
3.774
3.754
3.733
3.731
3.683
3.663
3.396
3.378
3.373
3.355
2.741
2.719
2.699
2.677
2.501
2.478
2.458
1.592
0.000
1.93
2.11
0.84
3.14
0.95
1.03
1.06
1.00
1.00


X : parts per Million : Carbon13
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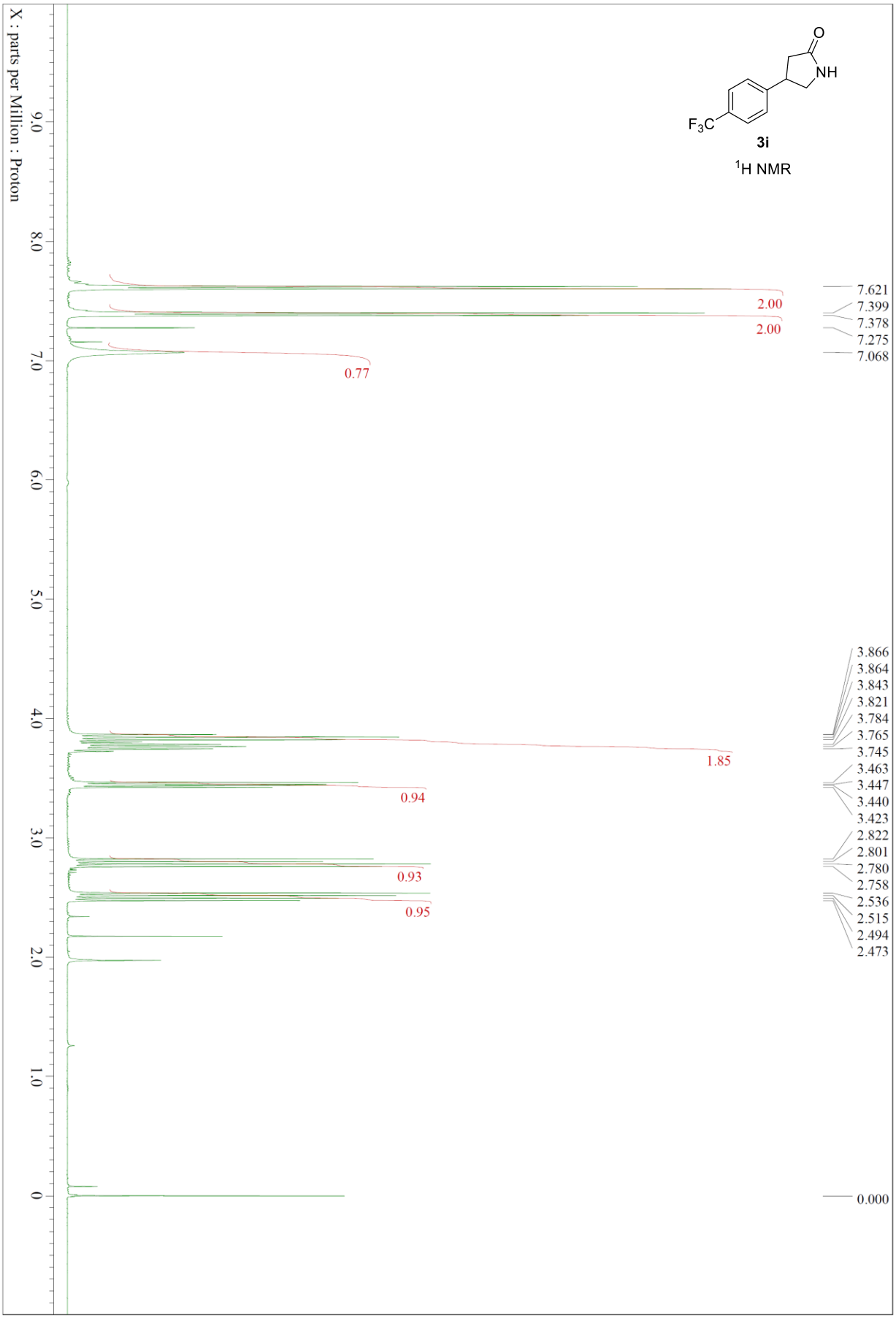
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
O
NH
MeO
3h
13C NMR
178.217
158.619
134.224
127.827
114.221
77.475
77.160
76.841
55.340
49.934
39.651
38.359


X : parts per Million : Proton
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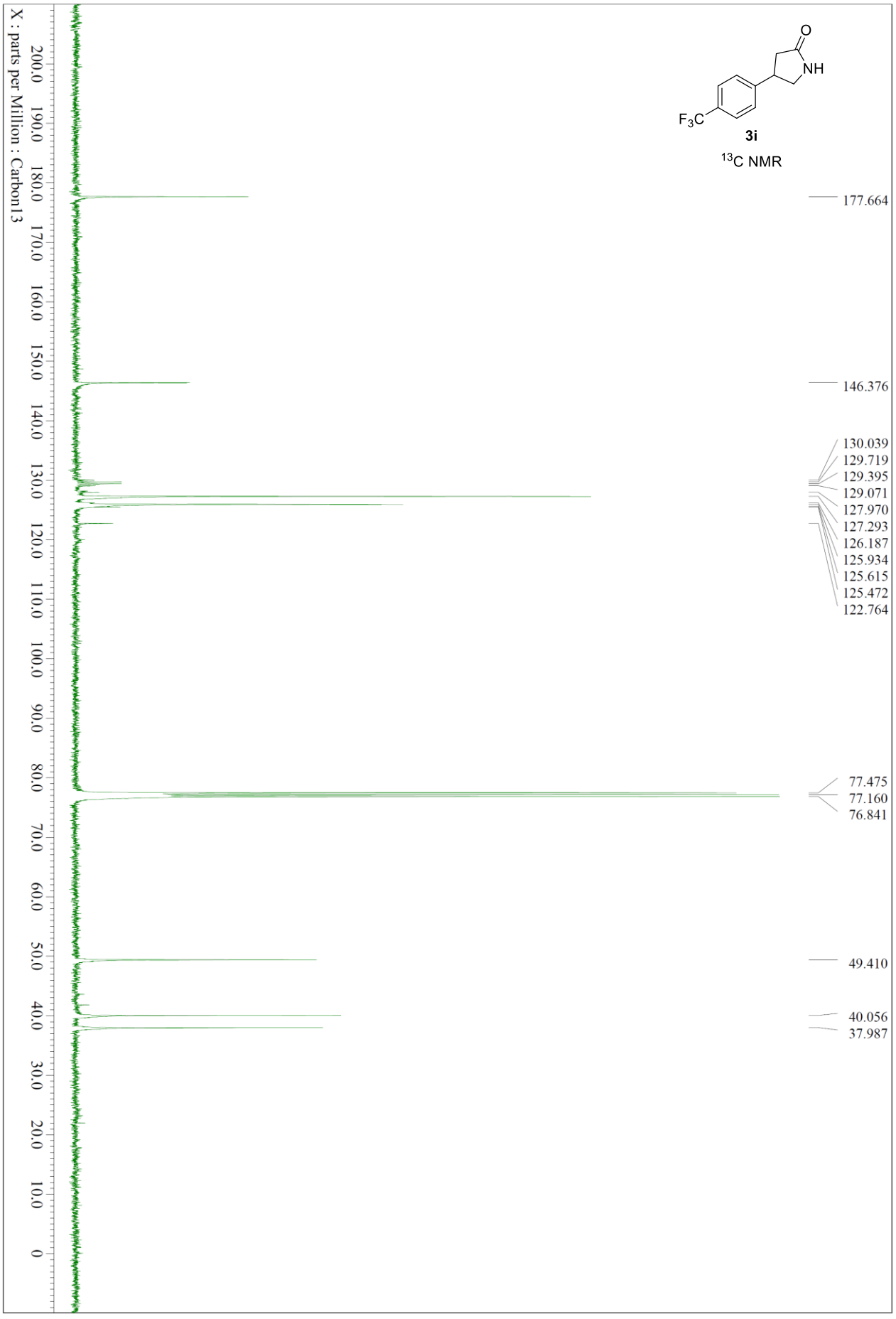
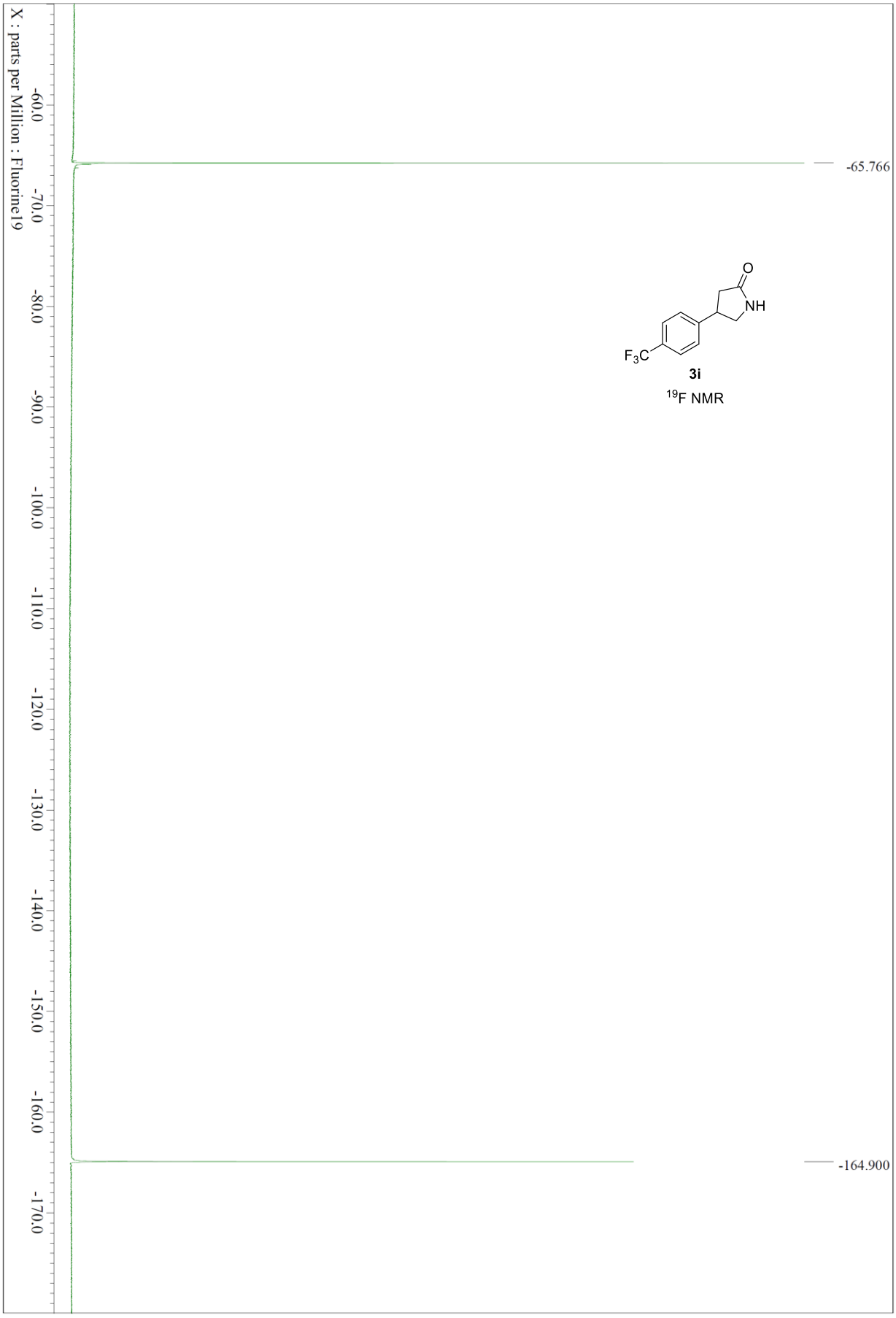
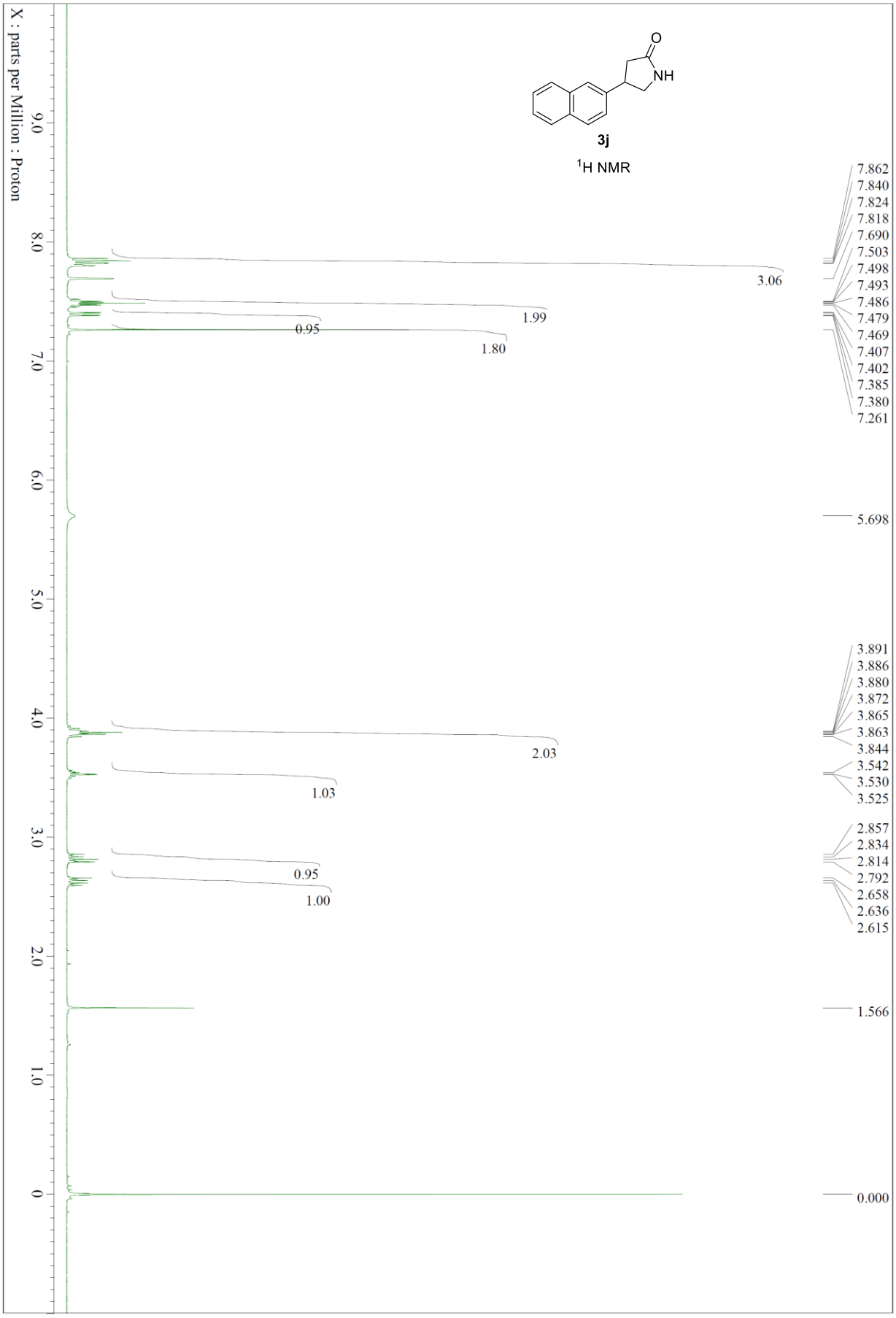
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
O
NH
F3C
3i
1H NMR
7.621
7.399
7.378
7.275
7.068
2.00
2.00
0.77
3.866
3.864
3.843
3.821
3.784
3.765
3.745
3.463
3.447
3.440
3.423
2.822
2.801
2.780
2.758
2.536
2.515
2.494
2.473
1.85
0.94
0.93
0.95
0.000

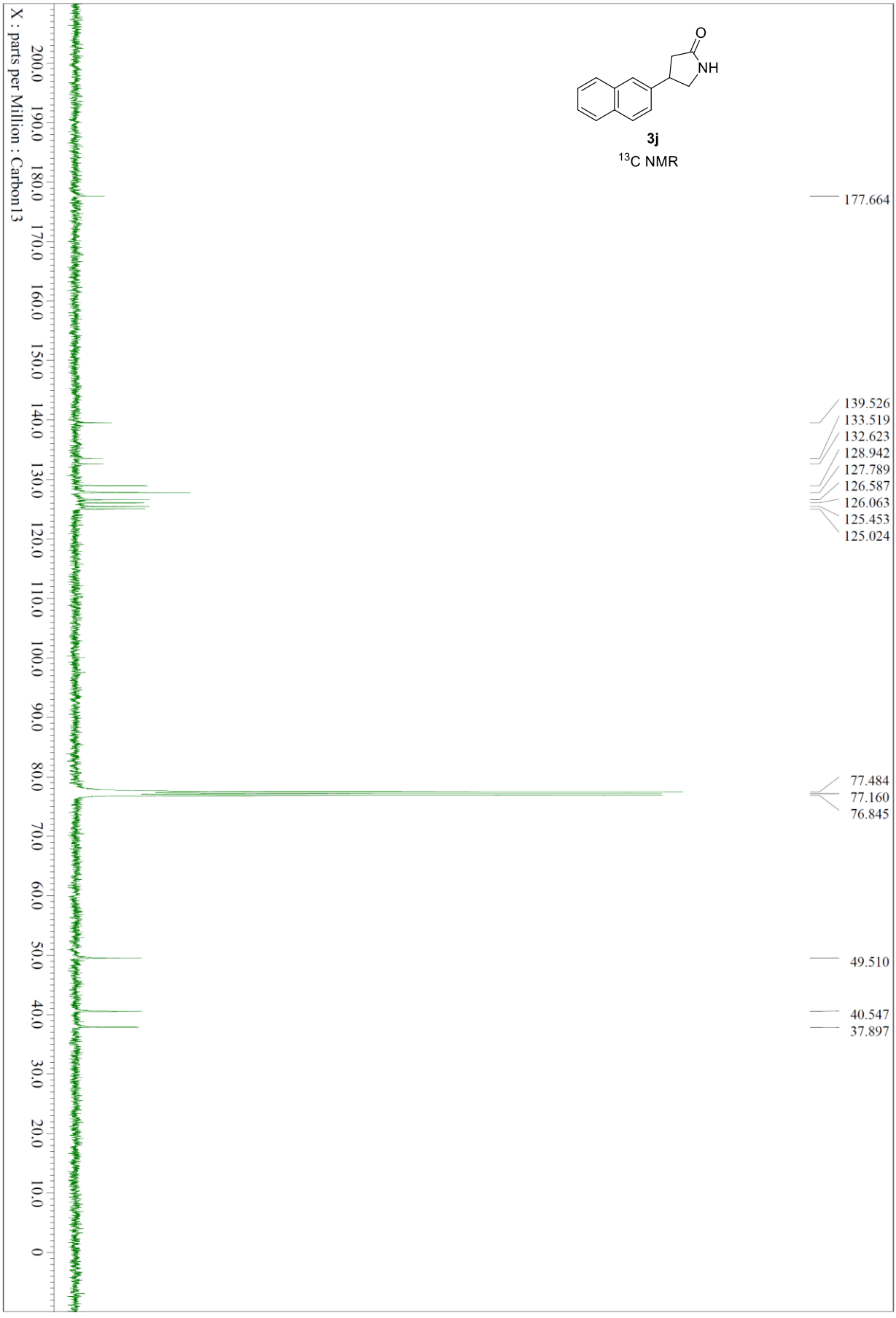

O
NH
F3C
3i
13C NMR
177.664
146.376
130.039
129.719
129.395
129.071
127.970
127.293
126.187
125.934
125.615
125.472
122.764
77.475
77.160
76.841
49.410
40.056
37.987
X : parts per Million : Carbon13
200.0
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0

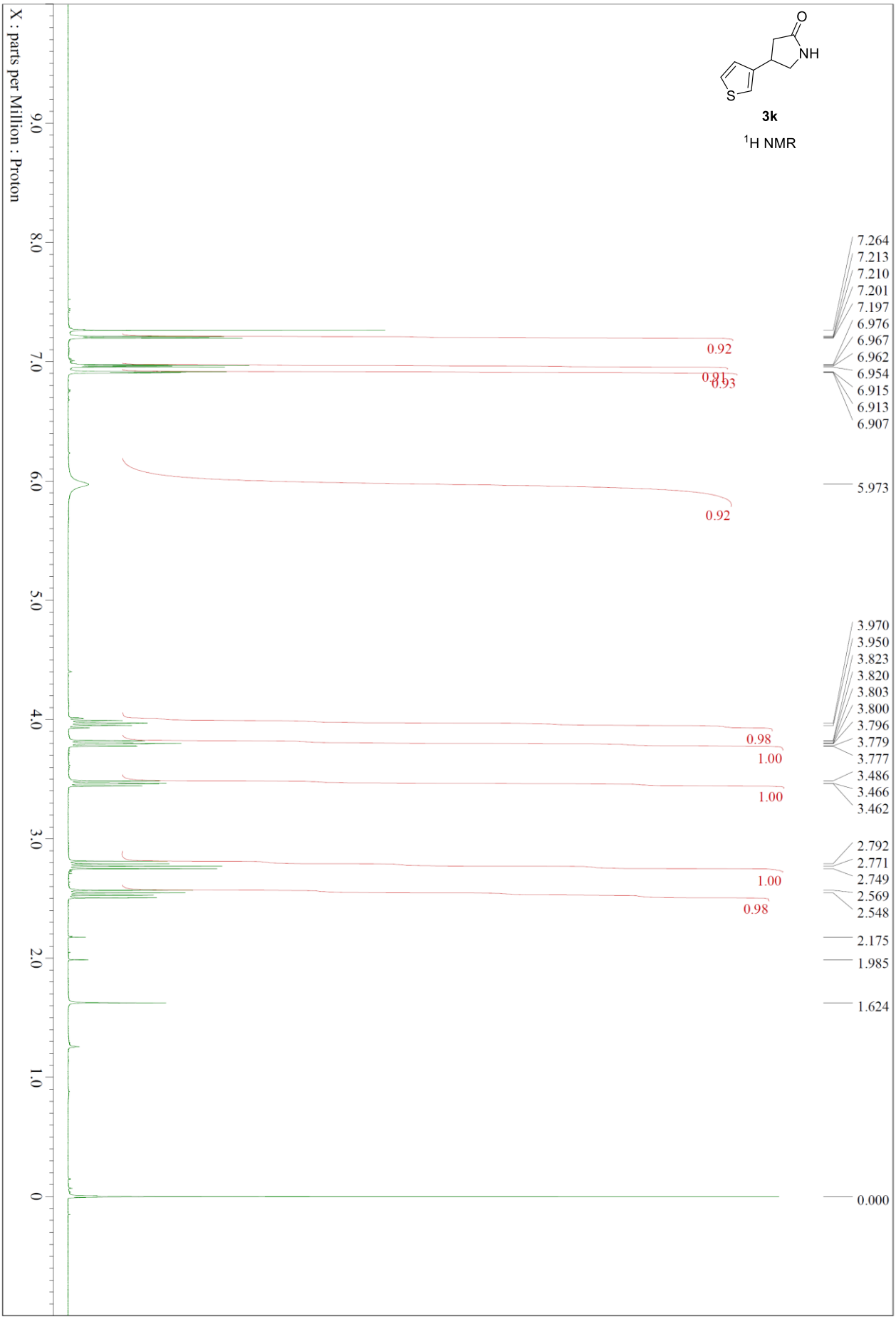

X : parts per Million : Fluorine19
-60.0
-70.0
-80.0
-90.0
-100.0
-110.0
-120.0
-130.0
-140.0
-150.0
-160.0
-170.0
-65.766
-164.900
O
NH
F3C

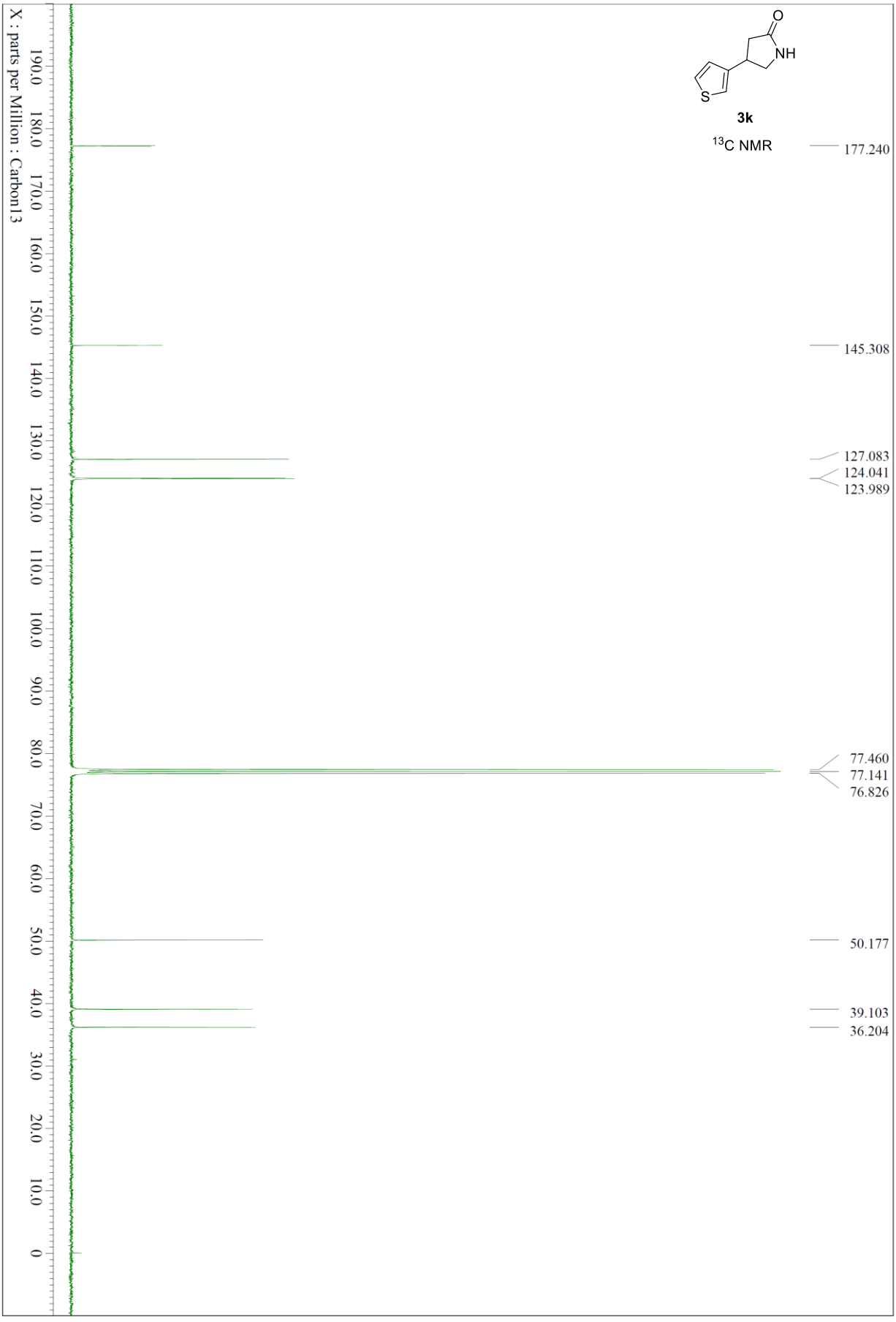
3i

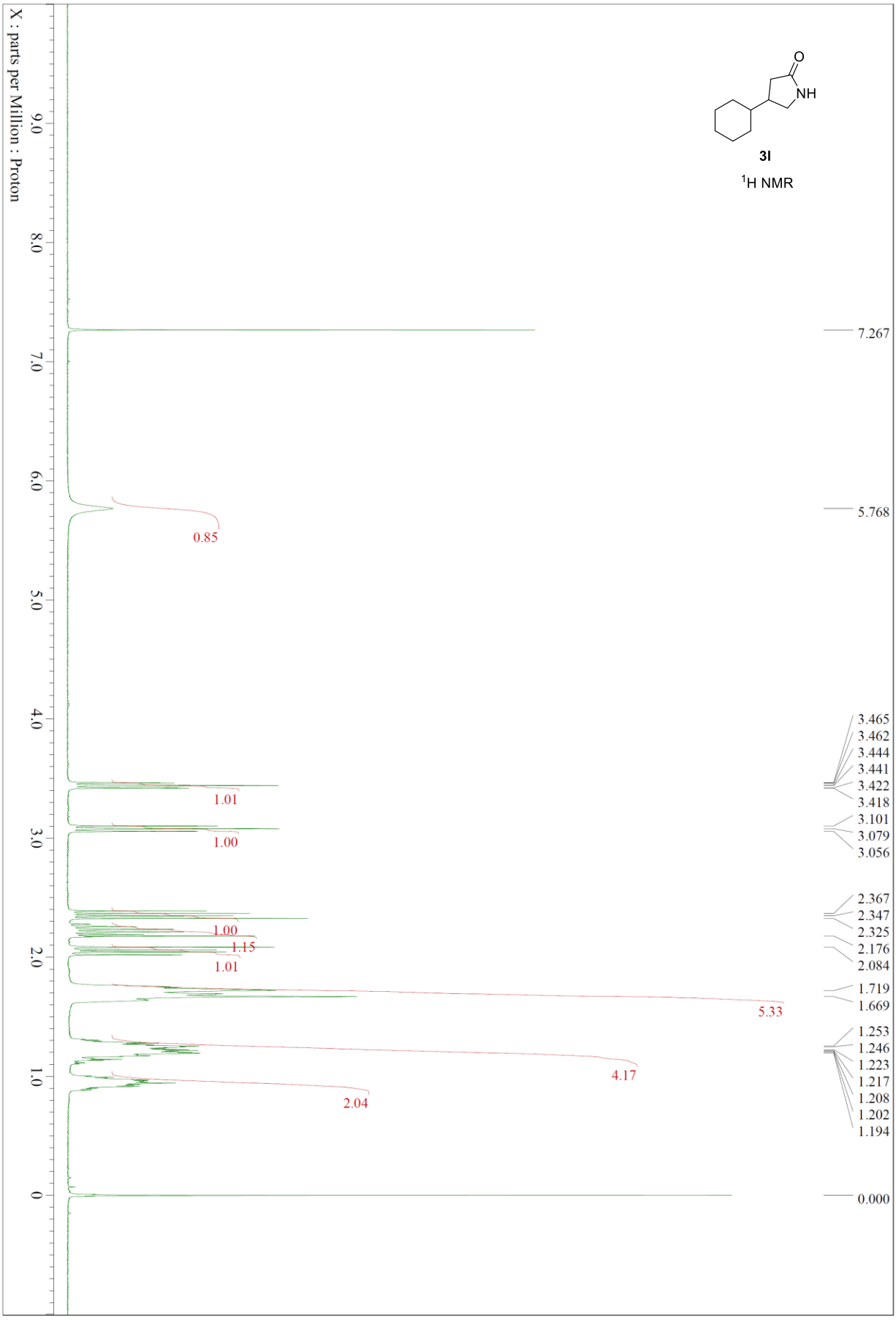
^{19}F NMR


X : parts per Million : Proton
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
O
NH
3j
1H NMR
7.862
7.840
7.824
7.818
7.690
7.503
7.498
7.493
7.486
7.479
7.469
7.407
7.402
7.385
7.380
7.261
5.698
3.891
3.886
3.880
3.872
3.865
3.863
3.844
3.542
3.530
3.525
2.857
2.834
2.814
2.792
2.658
2.636
2.615
1.566
0.000
3.06
1.99
0.95
1.80
2.03
1.03
0.95
1.00


O
NH
3j
13C NMR
177.664
139.526
133.519
132.623
128.942
127.789
126.587
126.063
125.453
125.024
77.484
77.160
76.845
49.510
40.547
37.897
X : parts per Million : Carbon13
200.0
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0


X : parts per Million : Proton
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
O
NH
S
3k
1H NMR
7.264
7.213
7.210
7.201
7.197
6.976
6.967
6.962
6.954
6.915
6.913
6.907
5.973
3.970
3.950
3.823
3.820
3.803
3.800
3.796
3.779
3.777
3.486
3.466
3.462
2.792
2.771
2.749
2.569
2.548
2.175
1.985
1.624
0.000
0.92
0.91
0.93
0.92
0.98
1.00
1.00
1.00
0.98


O
NH
S
3k
13C NMR
177.240
145.308
127.083
124.041
123.989
77.460
77.141
76.826
50.177
39.103
36.204
X : parts per Million : Carbon13
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0


X : parts per Million : Proton
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
O
NH
3l
1H NMR
7.267
5.768
3.465
3.462
3.444
3.441
3.422
3.418
3.101
3.079
3.056
2.367
2.347
2.325
2.176
2.084
1.719
1.669
1.253
1.246
1.223
1.217
1.208
1.202
1.194
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0.85
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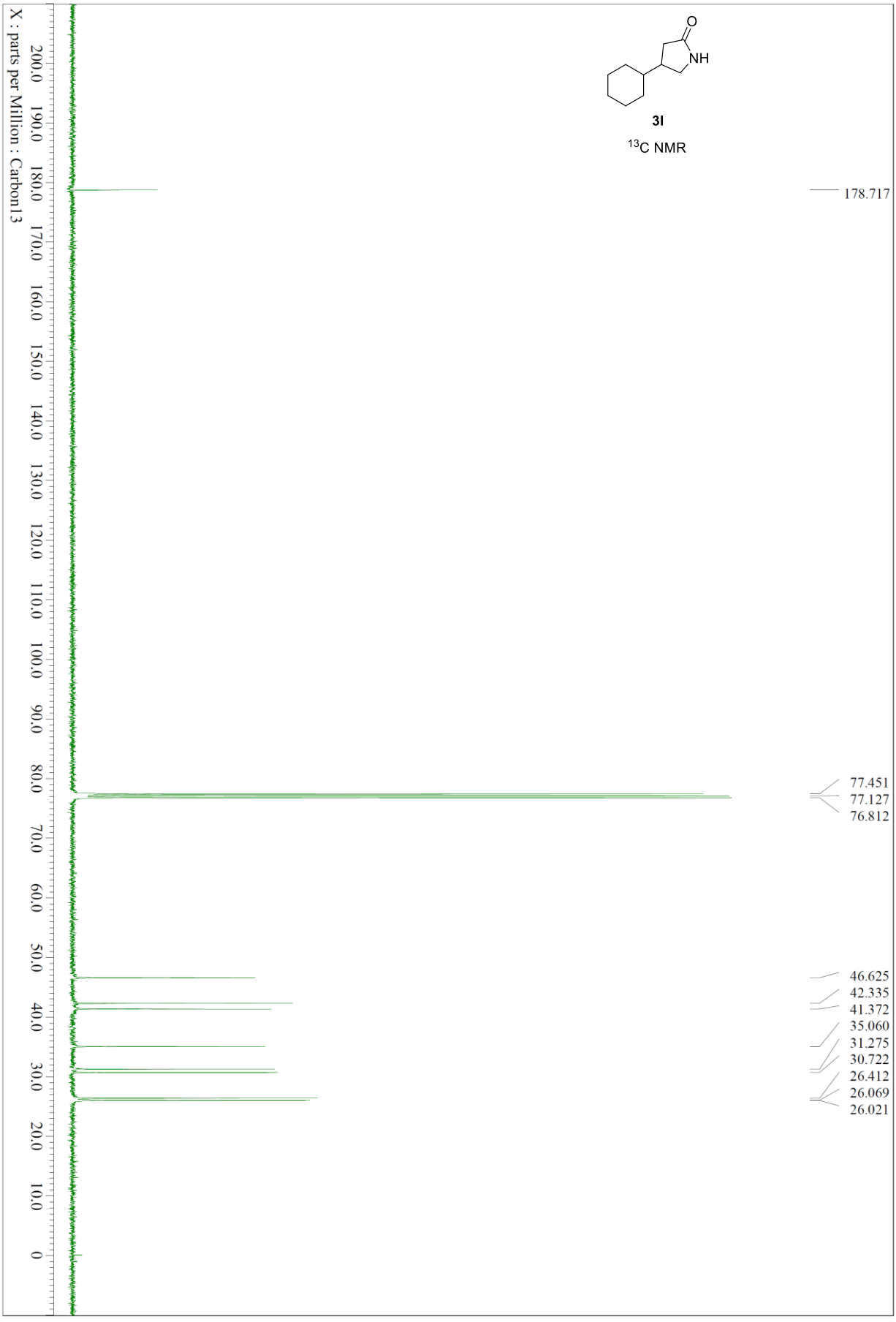
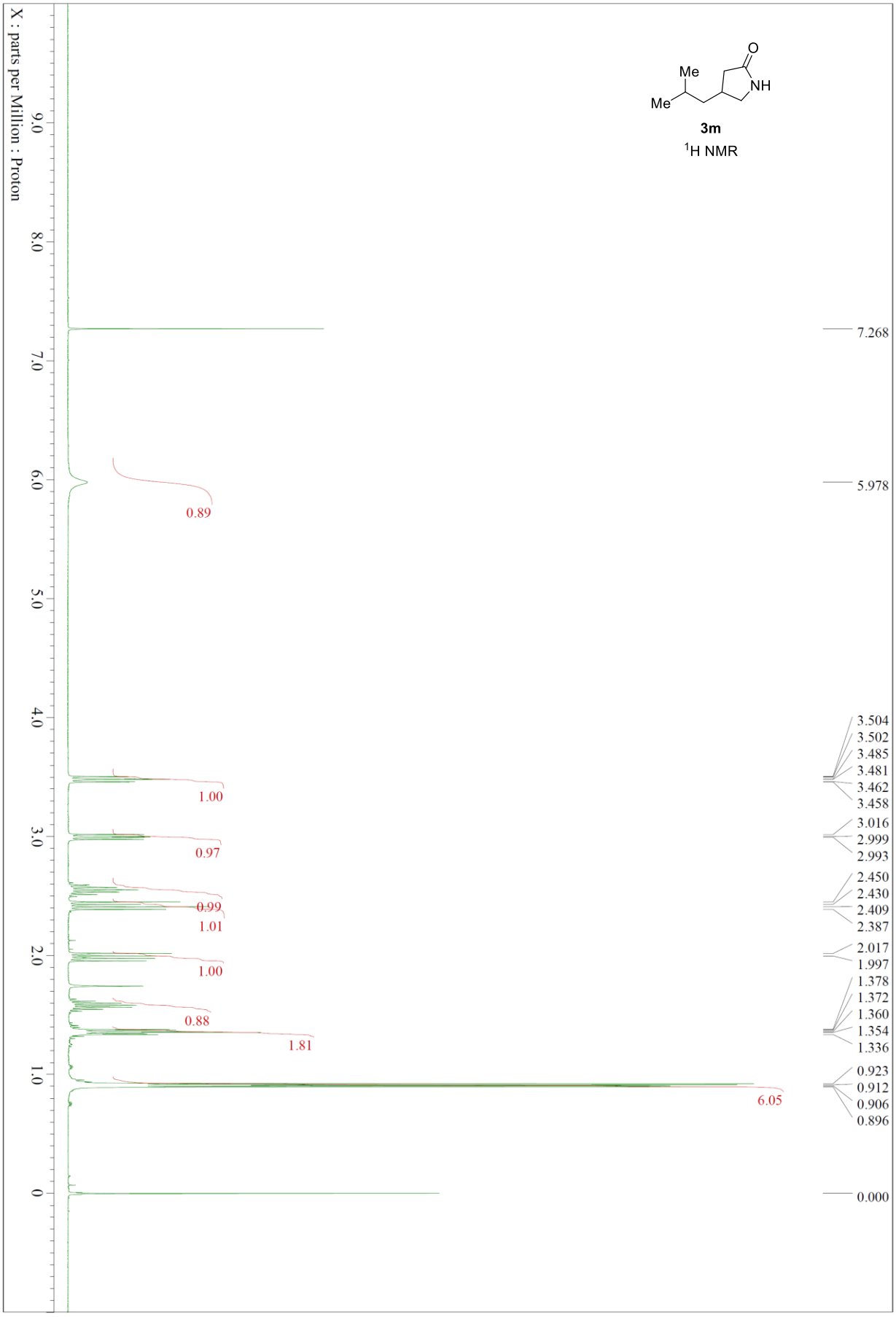
1.00
1.00
1.15
1.01
5.33
4.17
2.04


O
NH
3l
^{13}C NMR
178.717
77.451
77.127
76.812
46.625
42.335
41.372
35.060
31.275
30.722
26.412
26.069
26.021
X : parts per Million : Carbon13
200.0 190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0


X : parts per Million : Proton
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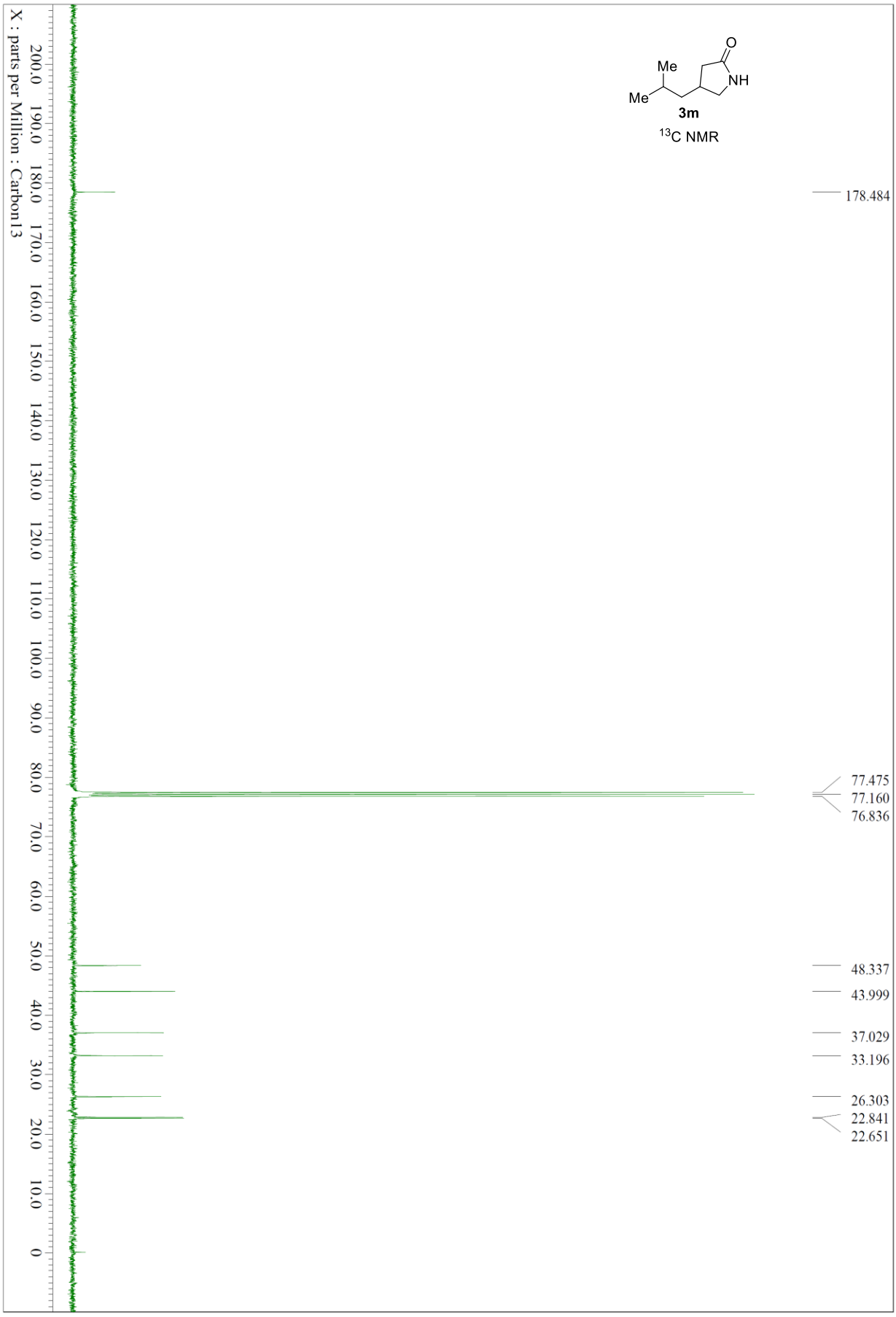
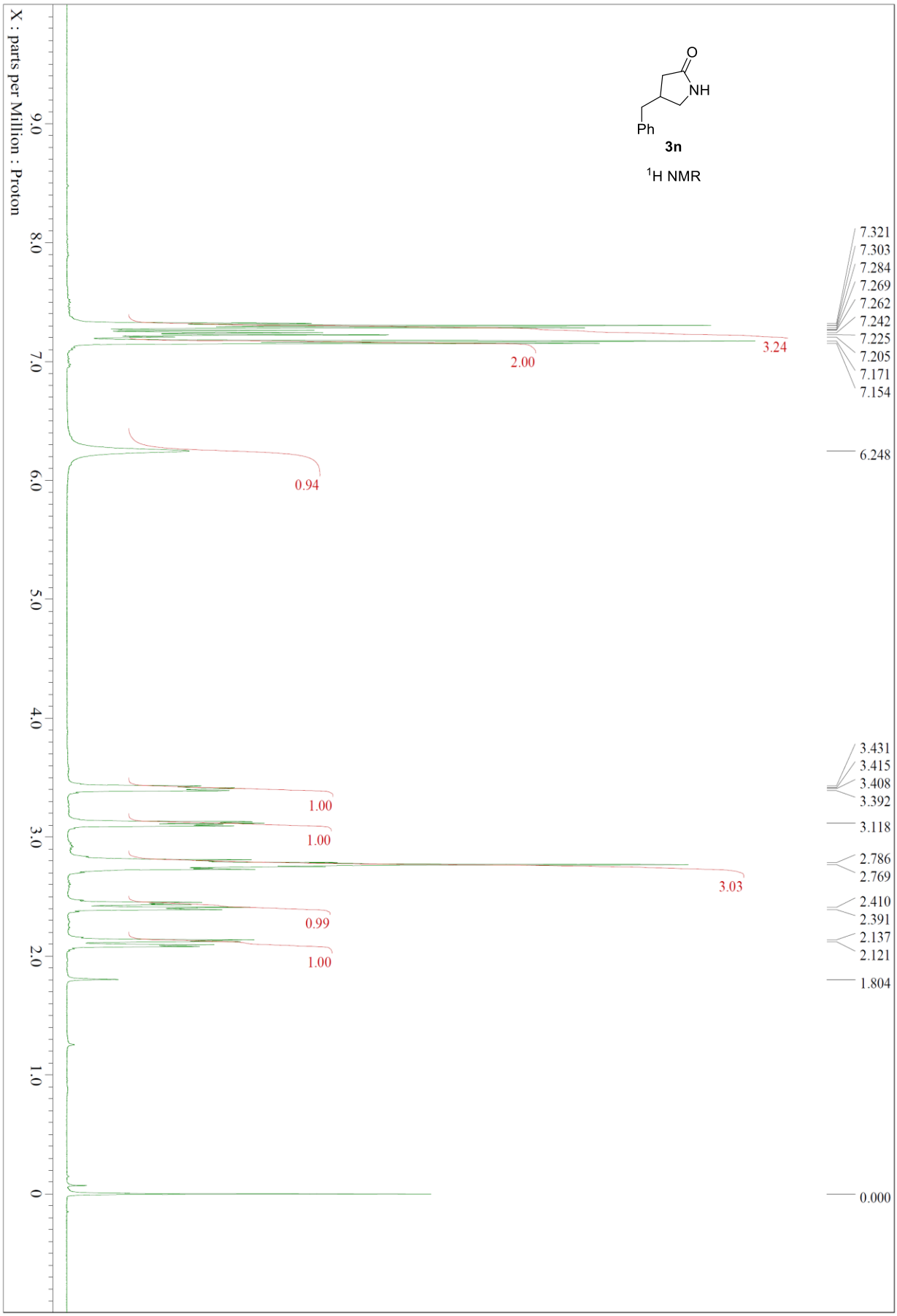
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
Me
Me
O
NH
3m
1H NMR
7.268
5.978
3.504
3.502
3.485
3.481
3.462
3.458
3.016
2.999
2.993
2.450
2.430
2.409
2.387
2.017
1.997
1.378
1.372
1.360
1.354
1.336
0.923
0.912
0.906
0.896
0.000
0.89
1.00
0.97
0.99
1.01
1.00
0.88
1.81
6.05


Me
Me
O
NH
3m
13C NMR
178.484
77.475
77.160
76.836
48.337
43.999
37.029
33.196
26.303
22.841
22.651
X : parts per Million : Carbon13
200.0
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0


X : parts per Million : Proton
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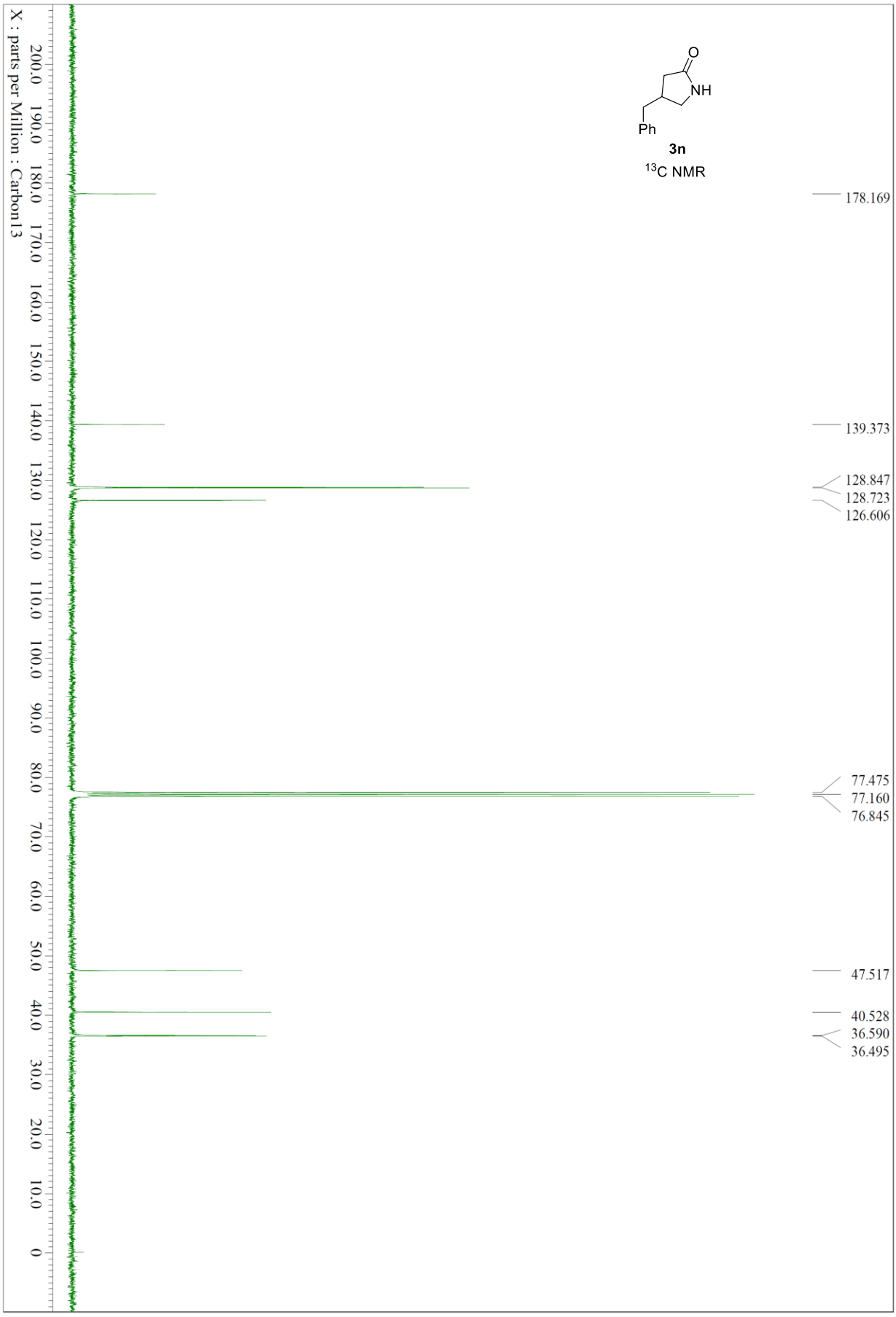
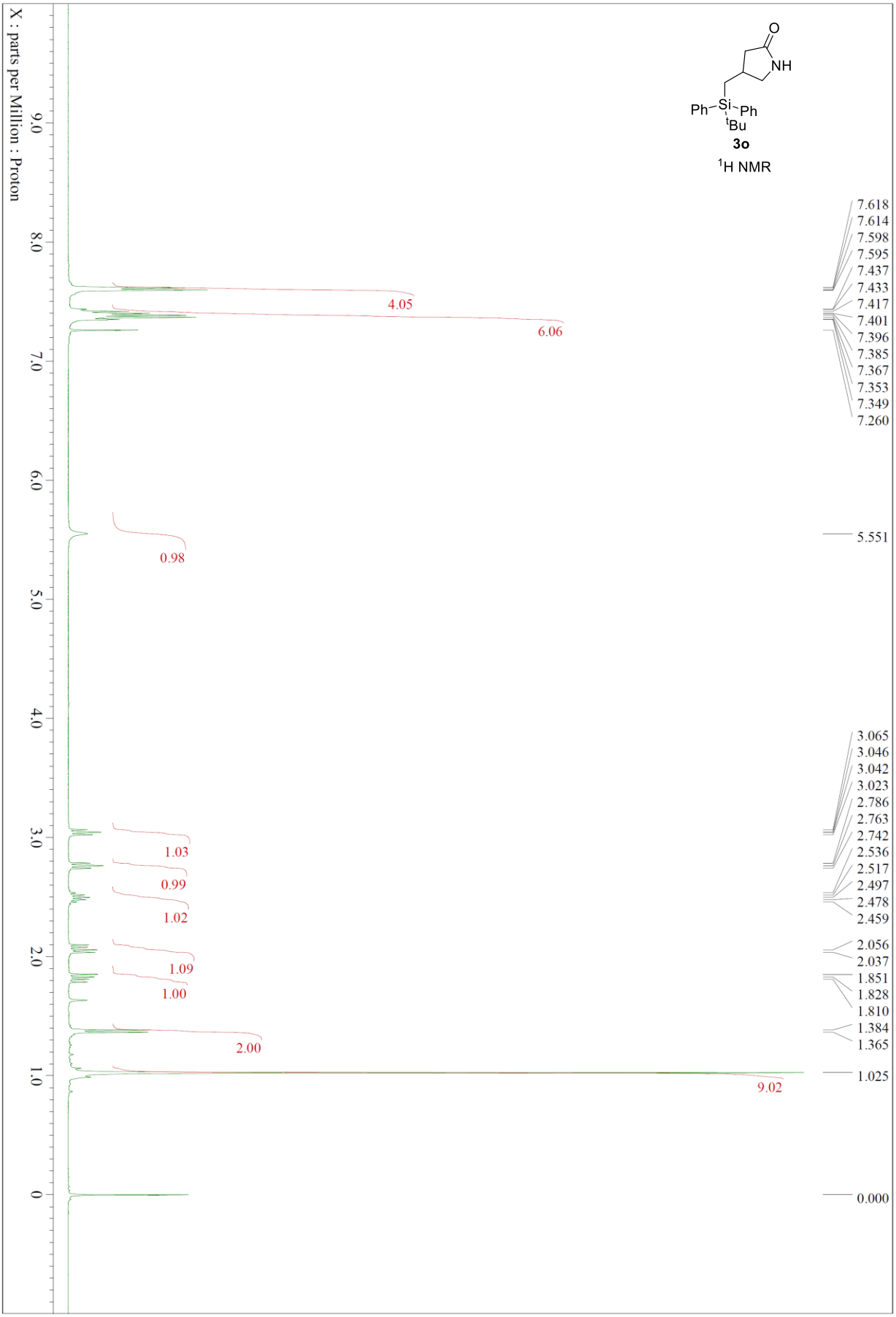
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
O
NH
Ph
3n
1H NMR
7.321
7.303
7.284
7.269
7.262
7.242
7.225
7.205
7.171
7.154
6.248
3.431
3.415
3.408
3.392
3.118
2.786
2.769
2.410
2.391
2.137
2.121
1.804
0.000
3.24
2.00
0.94
1.00
1.00
3.03
0.99
1.00


O
NH
Ph
3n
13C NMR
178.169
139.373
128.847
128.723
126.606
77.475
77.160
76.845
47.517
40.528
36.590
36.495
X : parts per Million : Carbon13
200.0
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0


X : parts per Million : Proton
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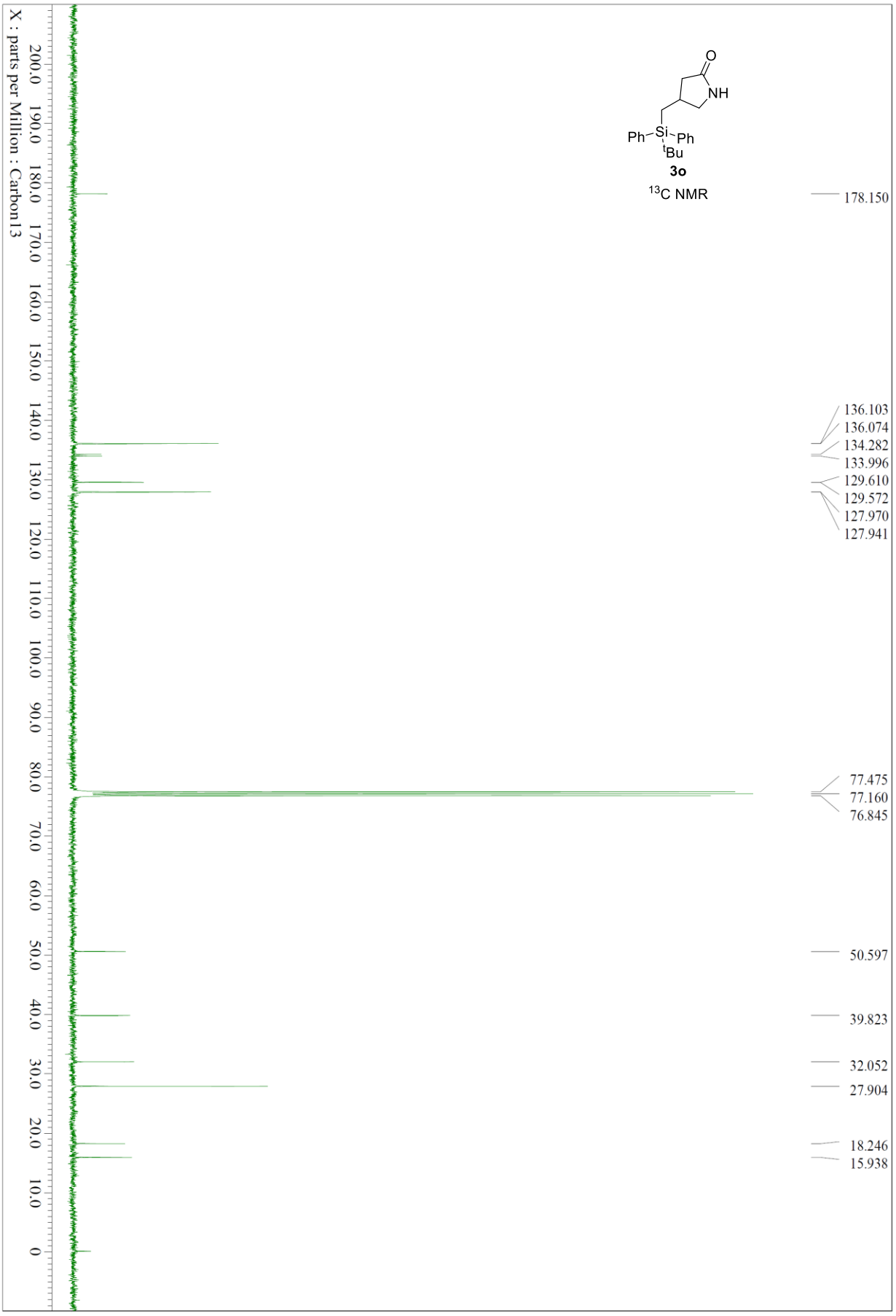
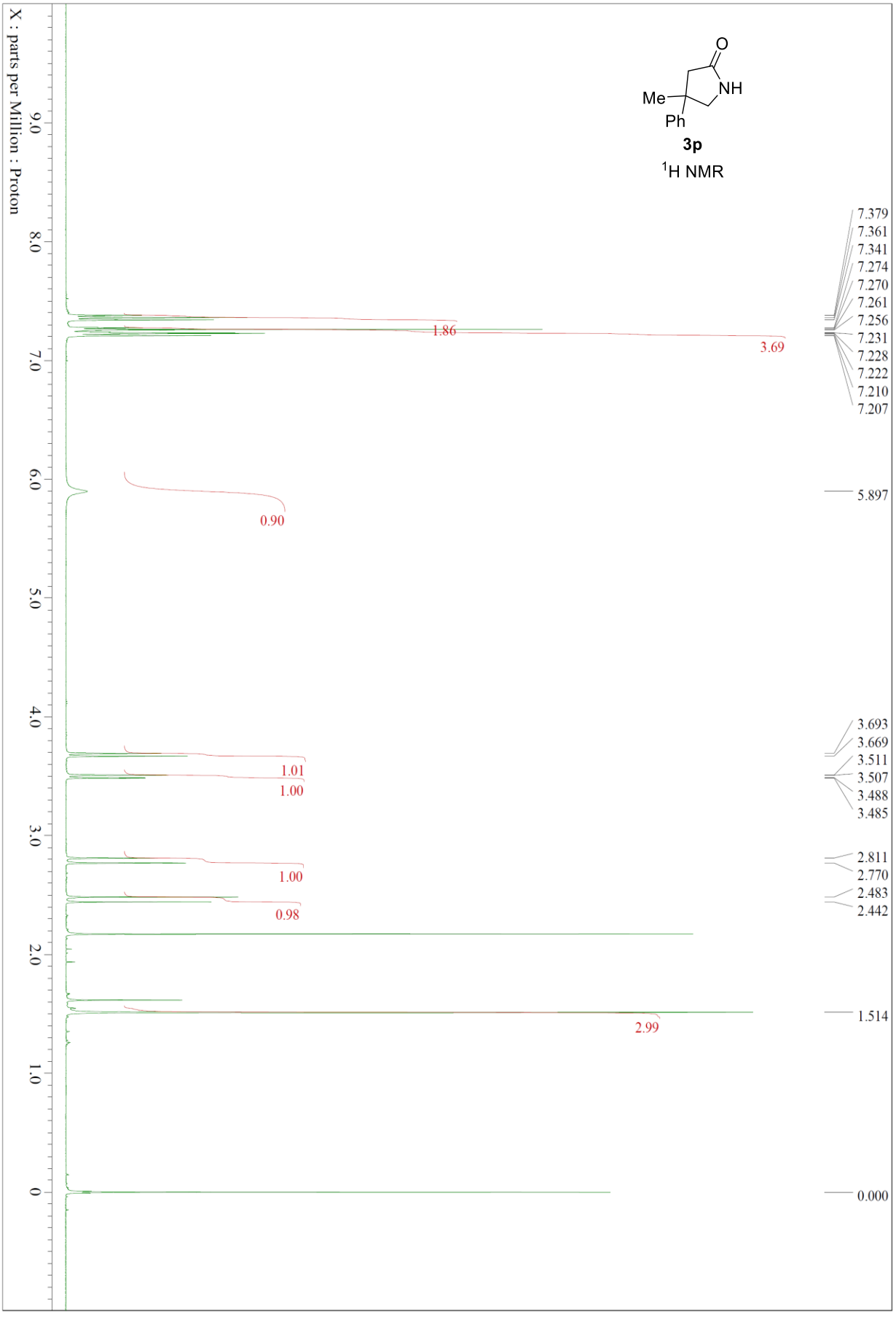
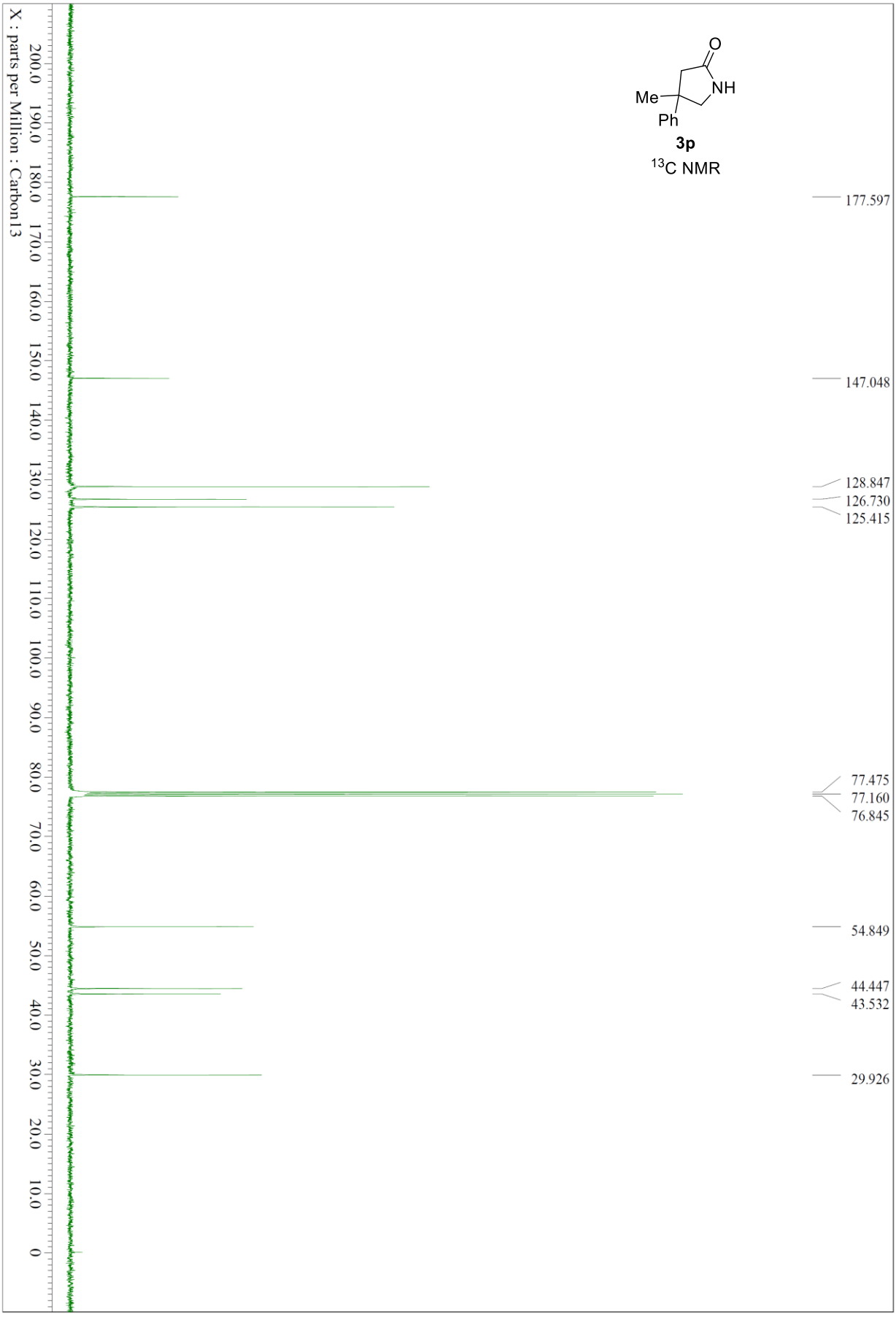
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
O
NH
Ph
Si
Ph
tBu
3o
1H NMR
4.05
6.06
0.98
1.03
0.99
1.02
1.09
1.00
2.00
9.02
7.618
7.614
7.598
7.595
7.437
7.433
7.417
7.401
7.396
7.385
7.367
7.353
7.349
7.260
5.551
3.065
3.046
3.042
3.023
2.786
2.763
2.742
2.536
2.517
2.497
2.478
2.459
2.056
2.037
1.851
1.828
1.810
1.384
1.365
1.025
0.000


O
NH
Ph
Si
Ph
tBu
3o
13C NMR
X : parts per Million : Carbon13
200.0
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
178.150
136.103
136.074
134.282
133.996
129.610
129.572
127.970
127.941
77.475
77.160
76.845
50.597
39.823
32.052
27.904
18.246
15.938


X : parts per Million : Proton
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
O
NH
Me
Ph
3p
1H NMR
7.379
7.361
7.341
7.274
7.270
7.261
7.256
7.231
7.228
7.222
7.210
7.207
5.897
3.693
3.669
3.511
3.507
3.488
3.485
2.811
2.770
2.483
2.442
1.514
0.000
1.86
3.69
0.90
1.01
1.00
1.00
0.98
2.99


X : parts per Million : Carbon13
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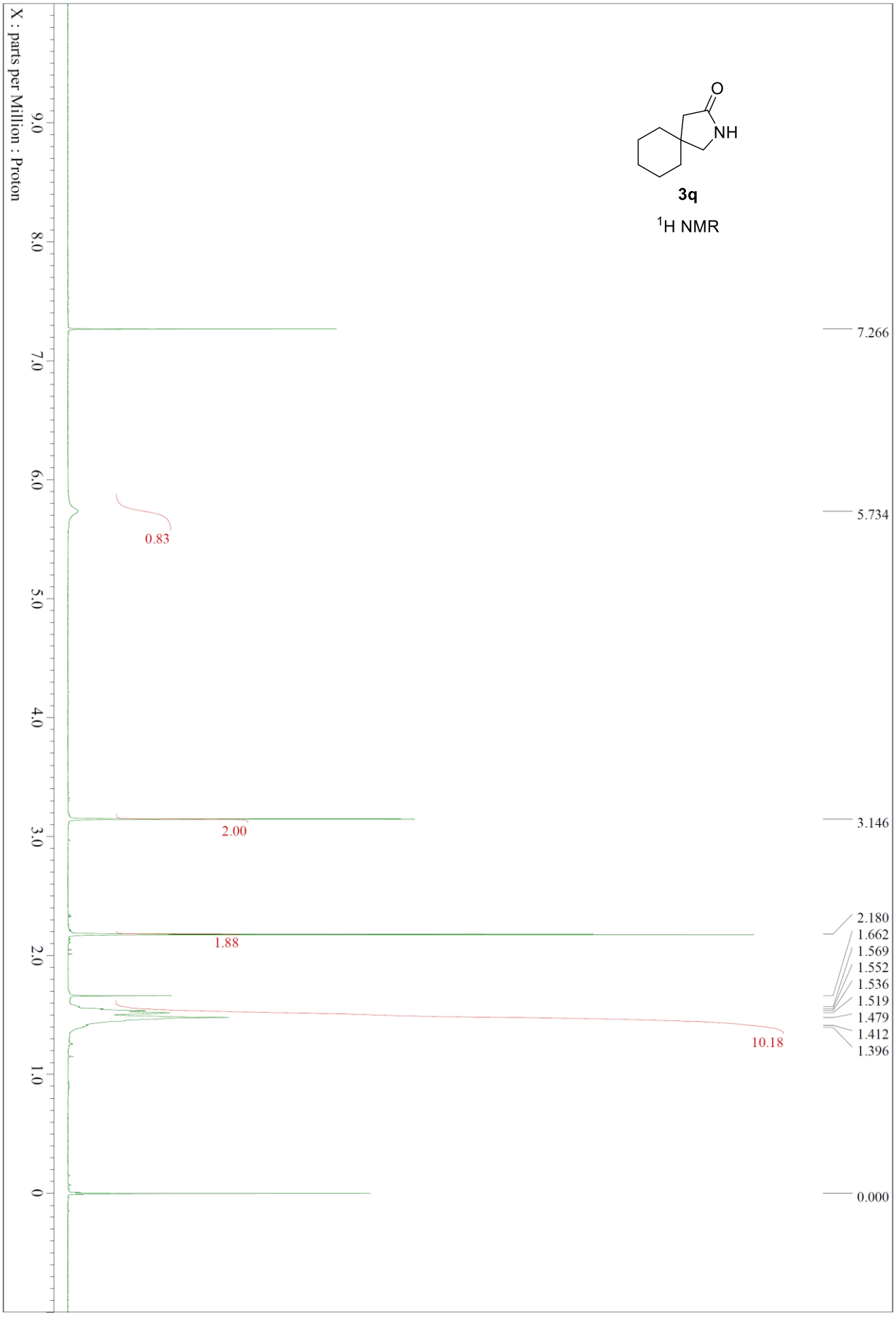
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
O
NH
Me
Ph
3p
13C NMR
177.597
147.048
128.847
126.730
125.415
77.475
77.160
76.845
54.849
44.447
43.532
29.926


X : parts per Million : Proton
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8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
O
NH
3q
1H NMR
7.266
5.734
3.146
2.180
1.662
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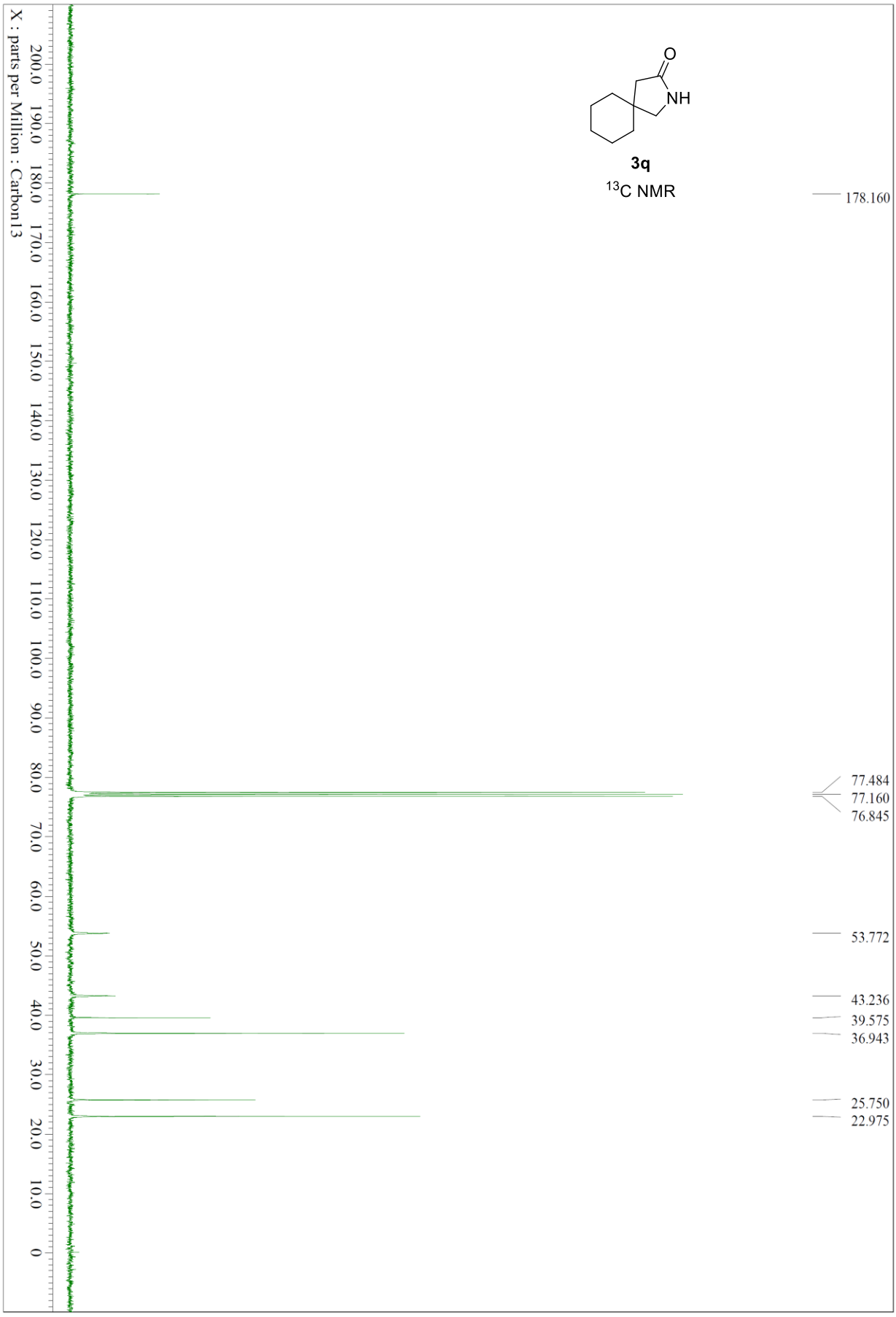
10.18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77.160
76.845
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25.750
22.975
X : parts per Million : Carbon13
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180.0
170.0
160.0
150.0
140.0
130.0
120.0
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80.0
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20.0
10.0
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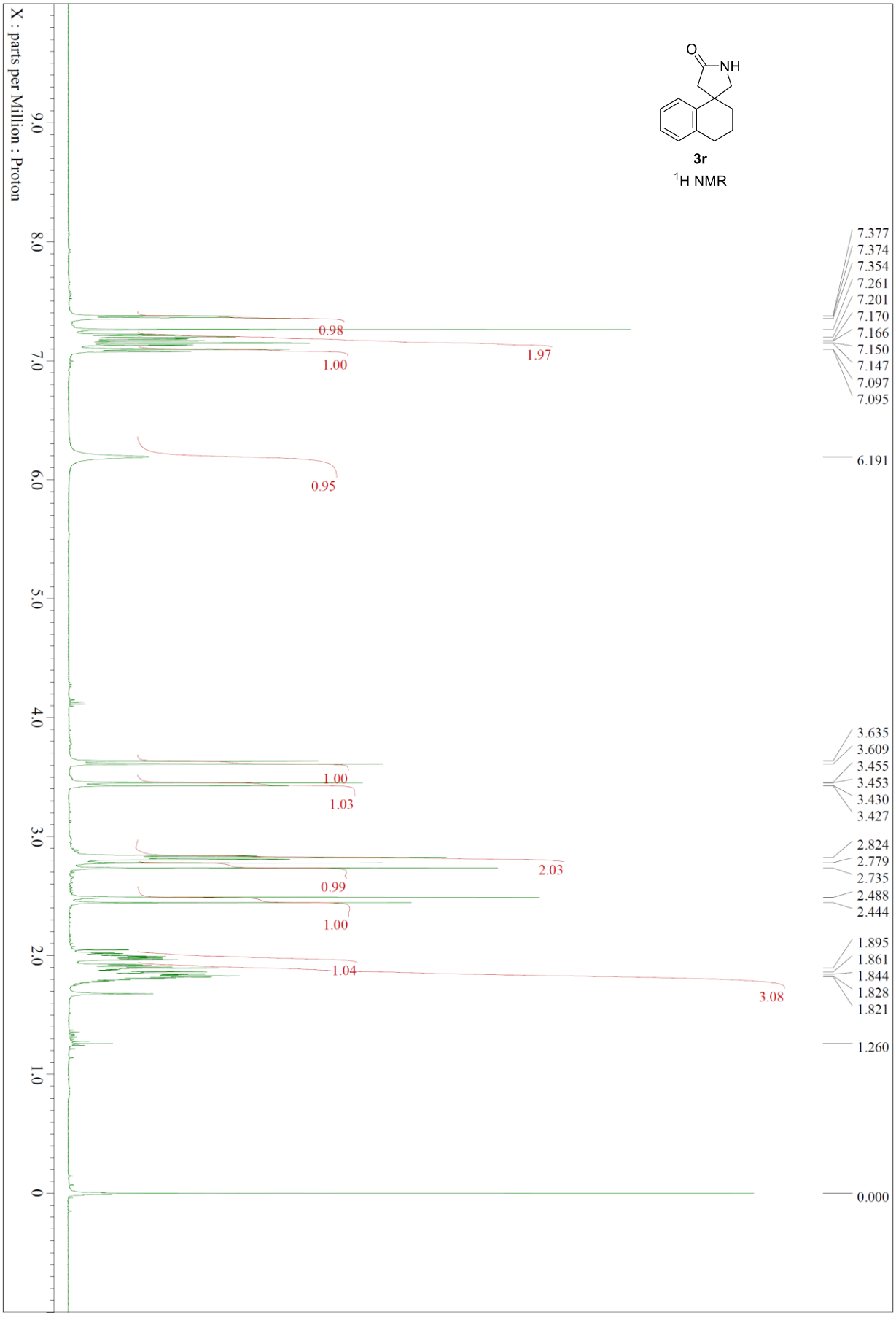
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0
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NH
3r
1H NMR
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7.374
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7.201
7.170
7.166
7.150
7.147
7.097
7.095
6.191
3.635
3.609
3.455
3.453
3.430
3.427
2.824
2.779
2.735
2.488
2.444
1.895
1.861
1.844
1.828
1.821
1.260
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1.00
0.95
1.00
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2.03
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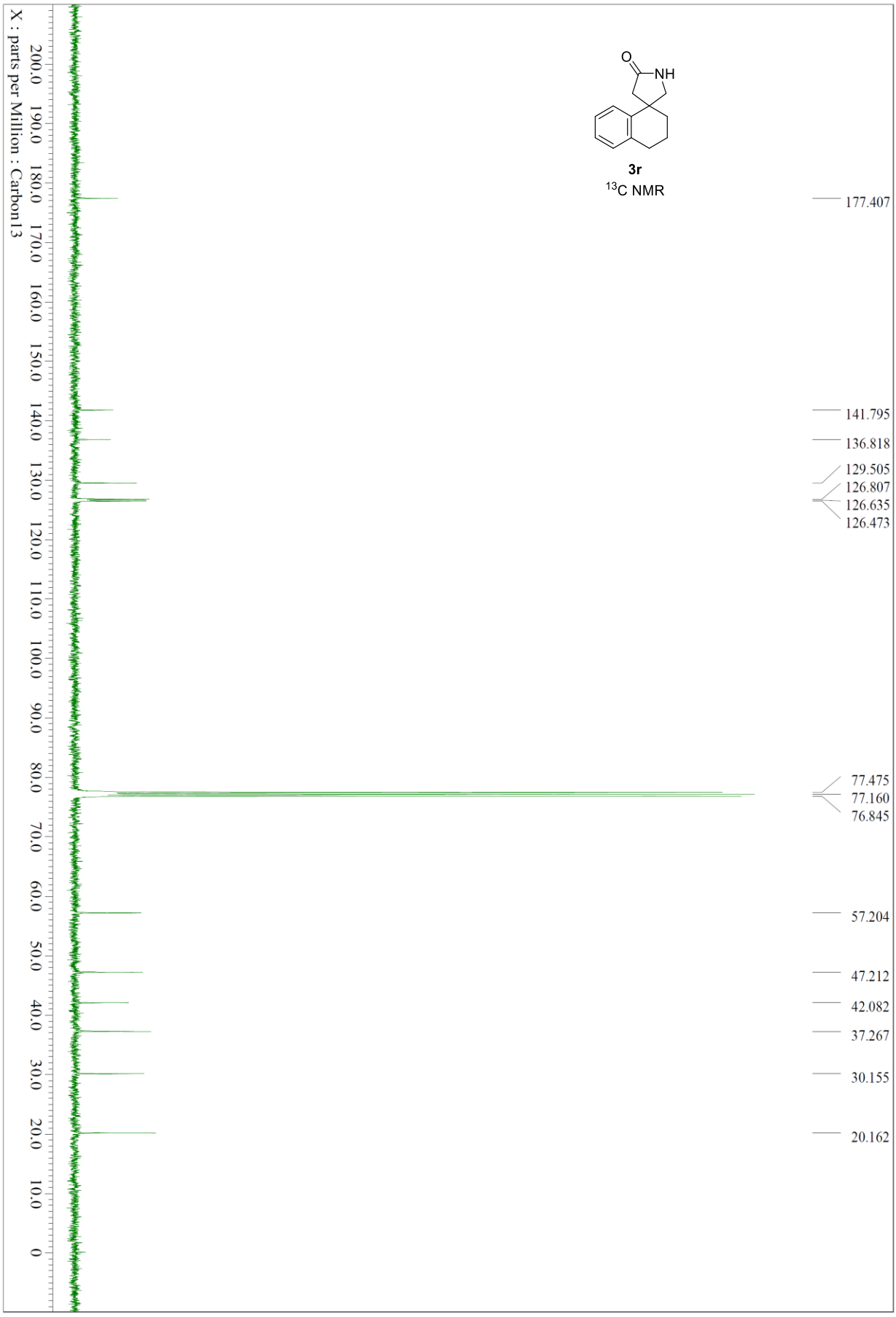
1.00
1.04
3.08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NH
3r
13C NMR
X : parts per Million : Carbon13
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140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
177.407
141.795
136.818
129.505
126.807
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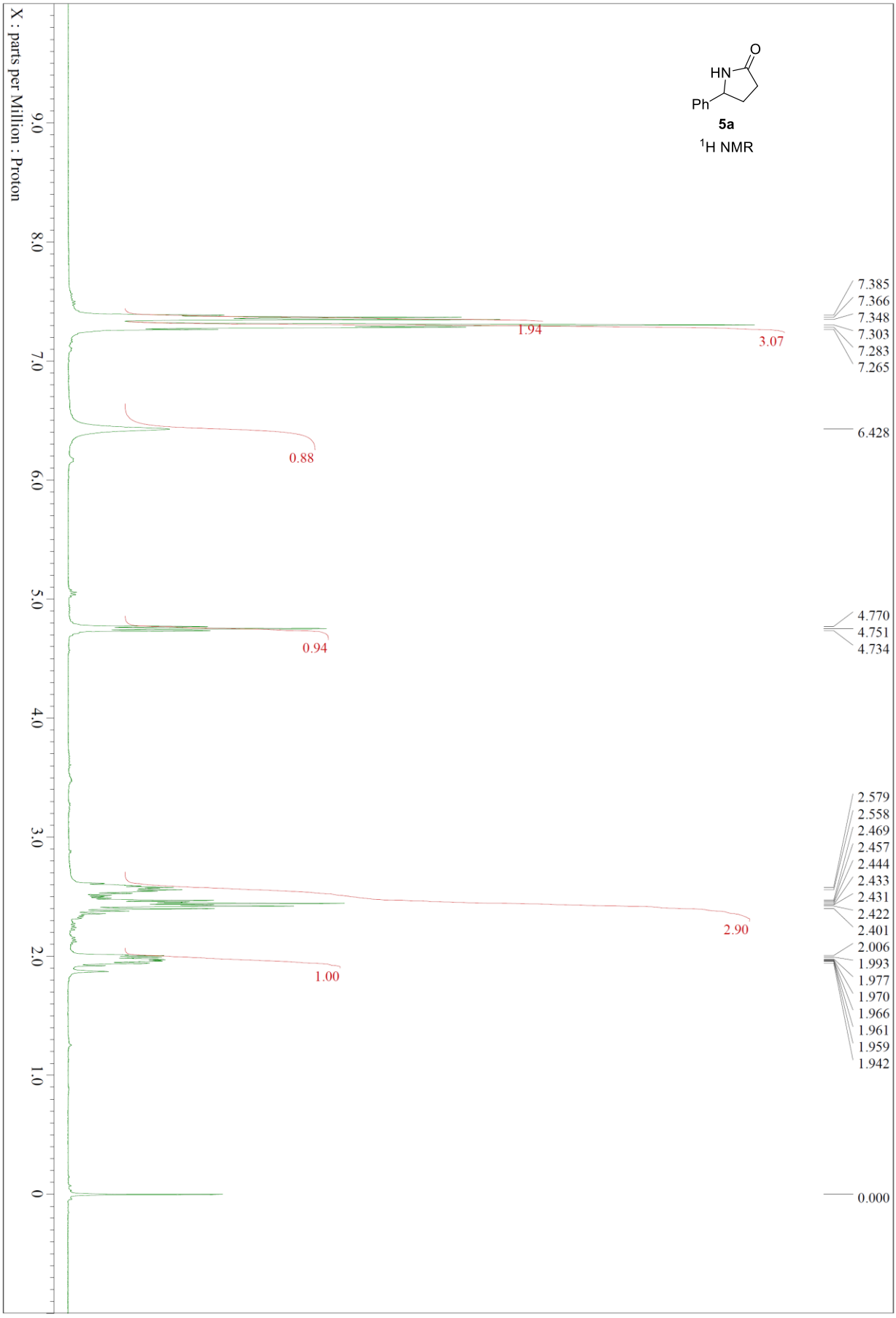
77.475
77.160
76.845
57.204
47.212
42.082
37.267
30.155
20.162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1.0
0
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HN
Ph
5a
1H NMR
7.385
7.366
7.348
7.303
7.283
7.265
6.428
4.770
4.751
4.734
2.579
2.558
2.469
2.457
2.444
2.433
2.431
2.422
2.401
2.006
1.993
1.977
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1.959
1.942
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3.07
0.88
0.94
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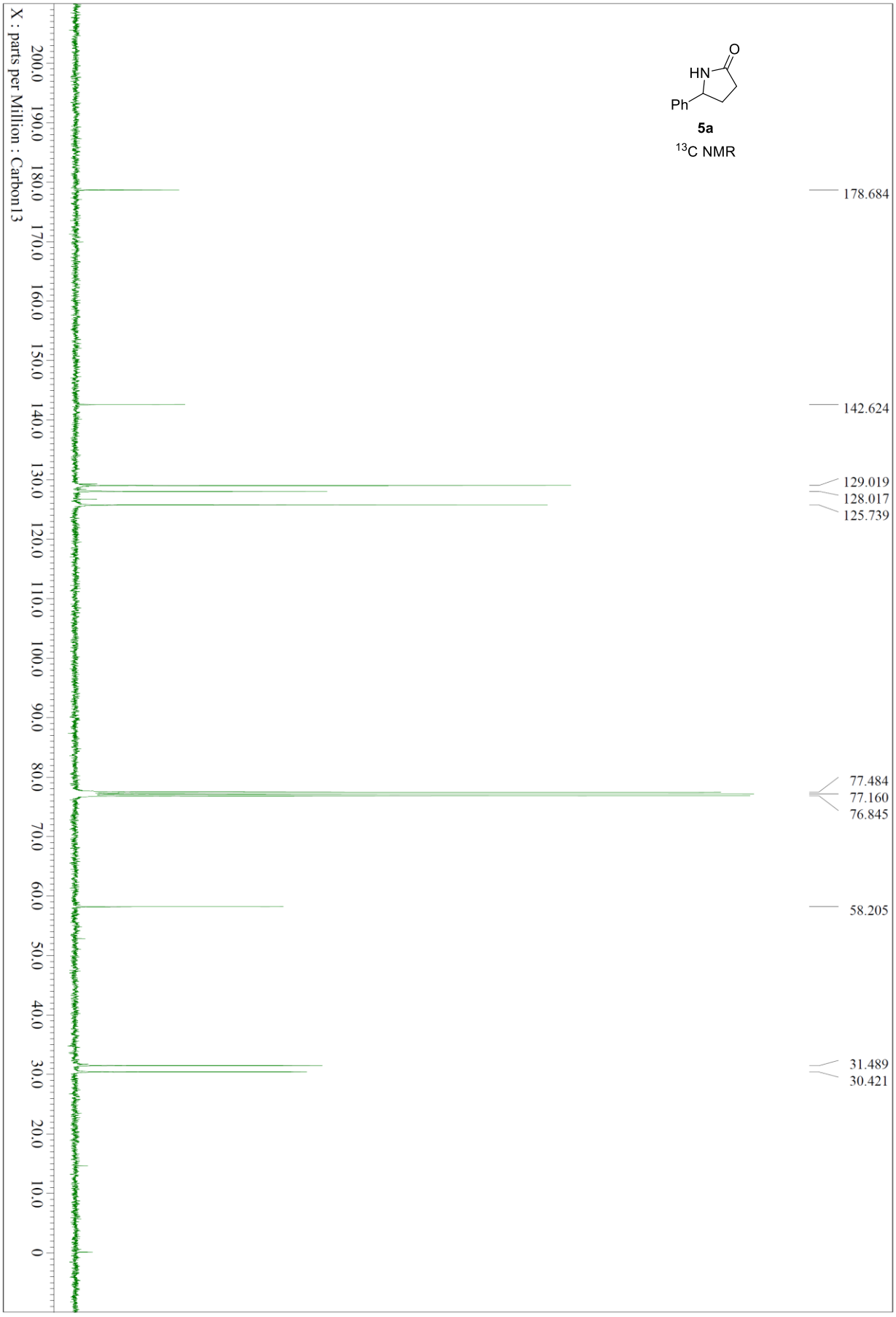
1.00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13C NMR
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77.160
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58.205
31.489
30.421
X : parts per Million : Carbon13
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140.0
130.0
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80.0
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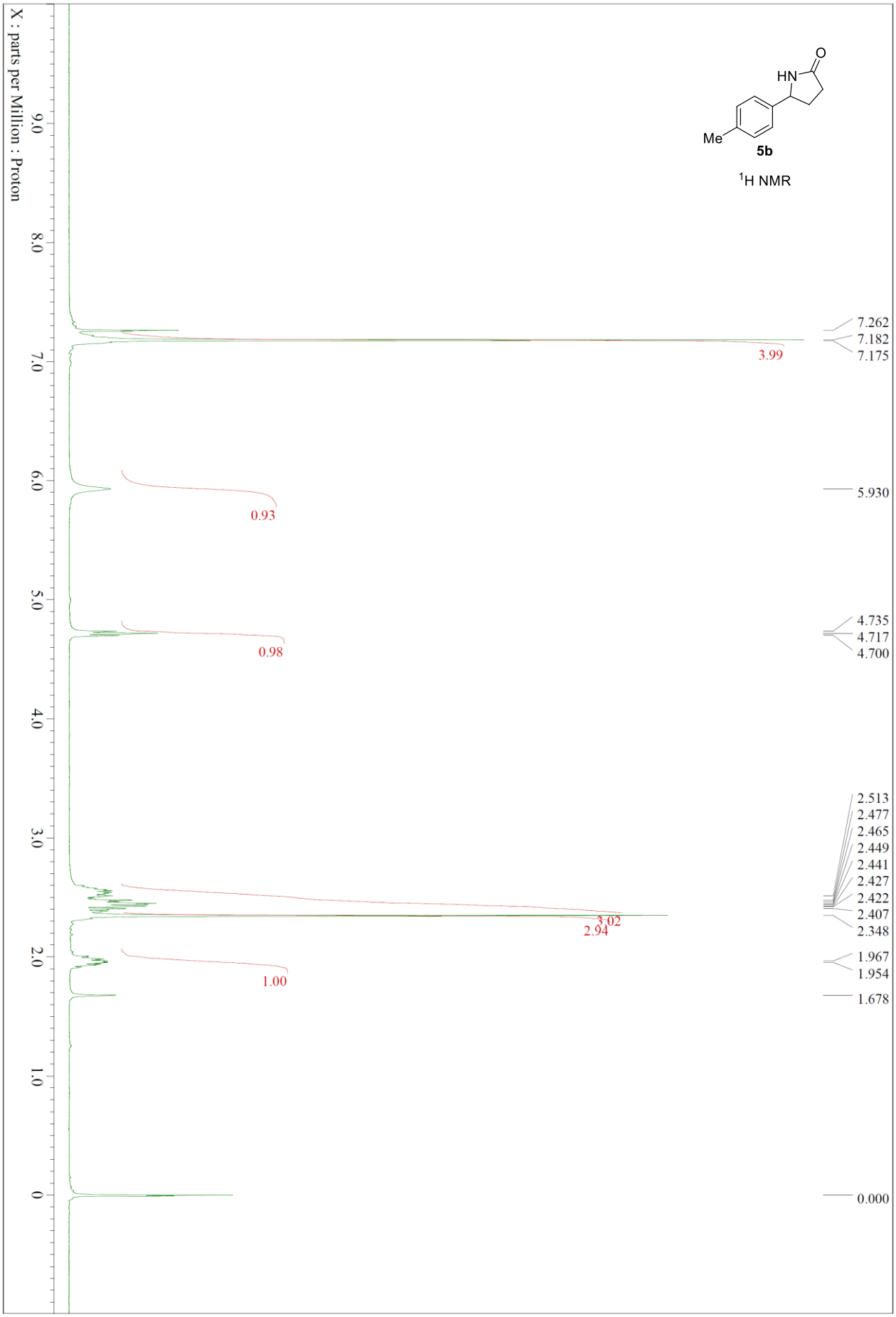
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5.0
4.0
3.0
2.0
1.0
0
HN
O
Me
5b
1H NMR
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7.182
7.175
3.99
5.930
0.93
4.735
4.717
4.700
0.98
2.513
2.477
2.465
2.449
2.441
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2.422
2.407
2.348
3.02
2.94
1.967
1.954
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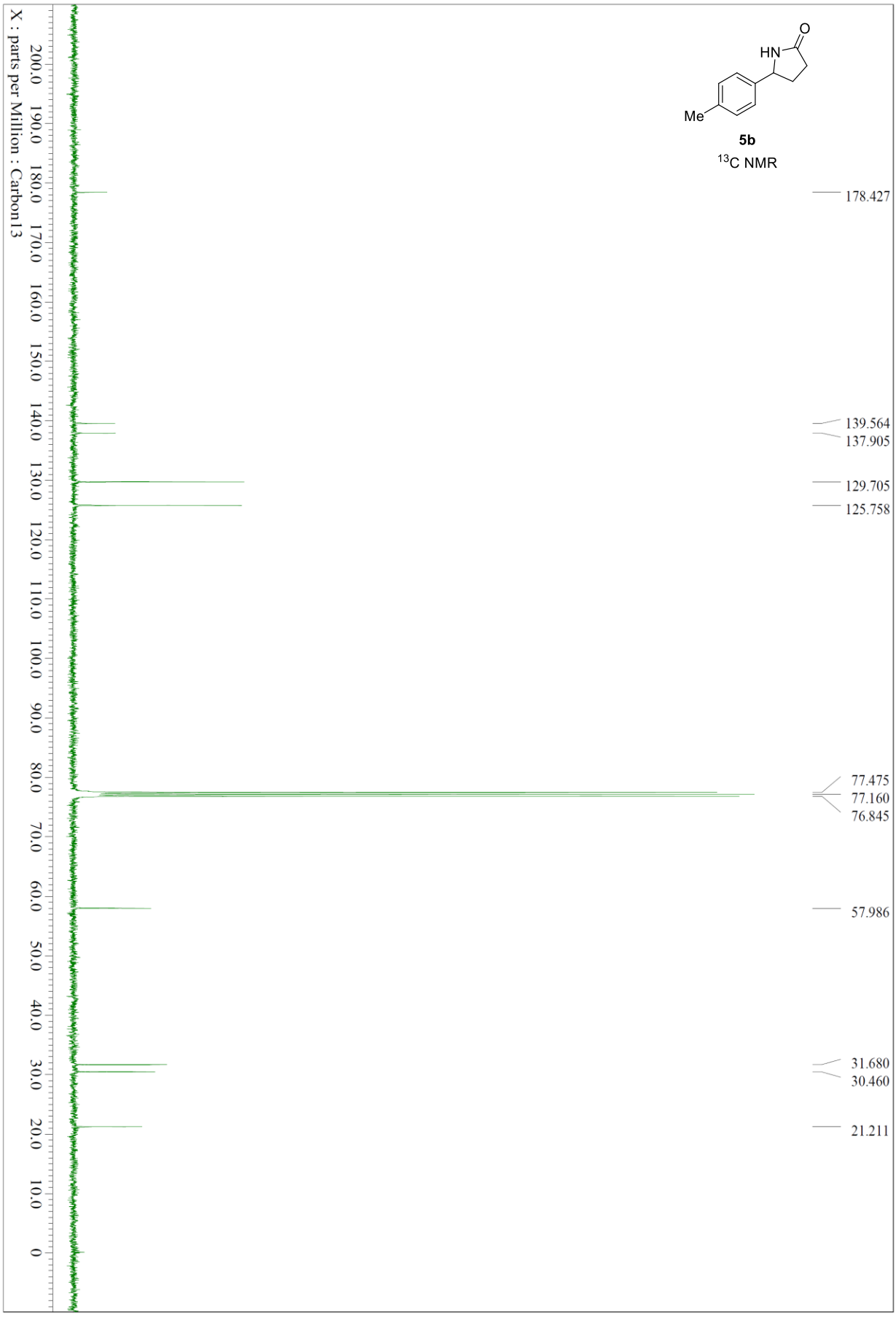
0.000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160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
HN
O
Me
5b
13C NMR
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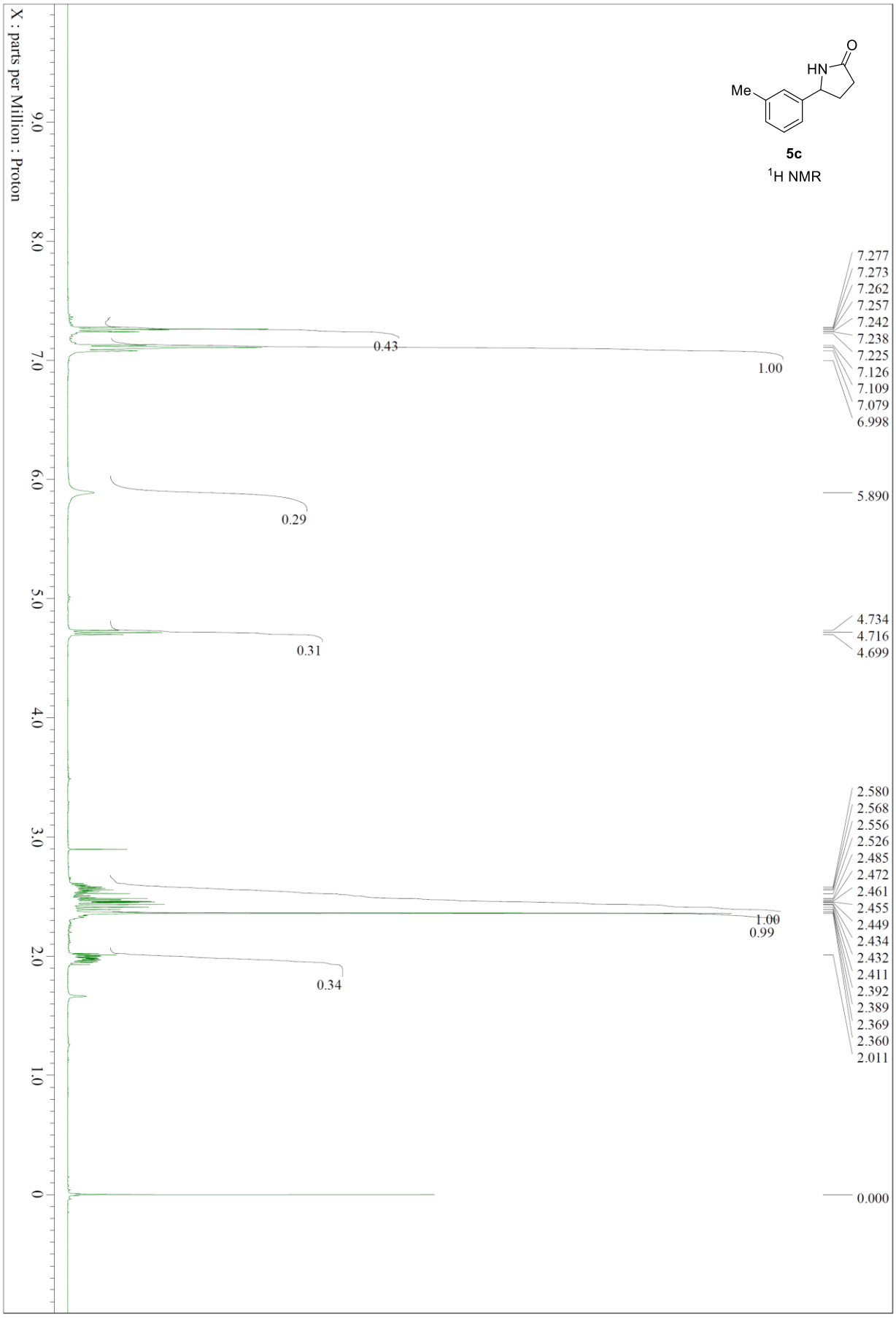
129.705
125.758
77.475
77.160
76.845
57.986
31.680
30.460
21.211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7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
O
HN
Me
5c
1H NMR
7.277
7.273
7.262
7.257
7.242
7.238
7.225
7.126
7.109
7.079
6.998
0.43
1.00
5.890
0.29
4.734
4.716
4.699
0.31
2.580
2.568
2.556
2.526
2.485
2.472
2.461
2.455
2.449
2.434
2.432
2.411
2.392
2.389
2.369
2.360
2.011
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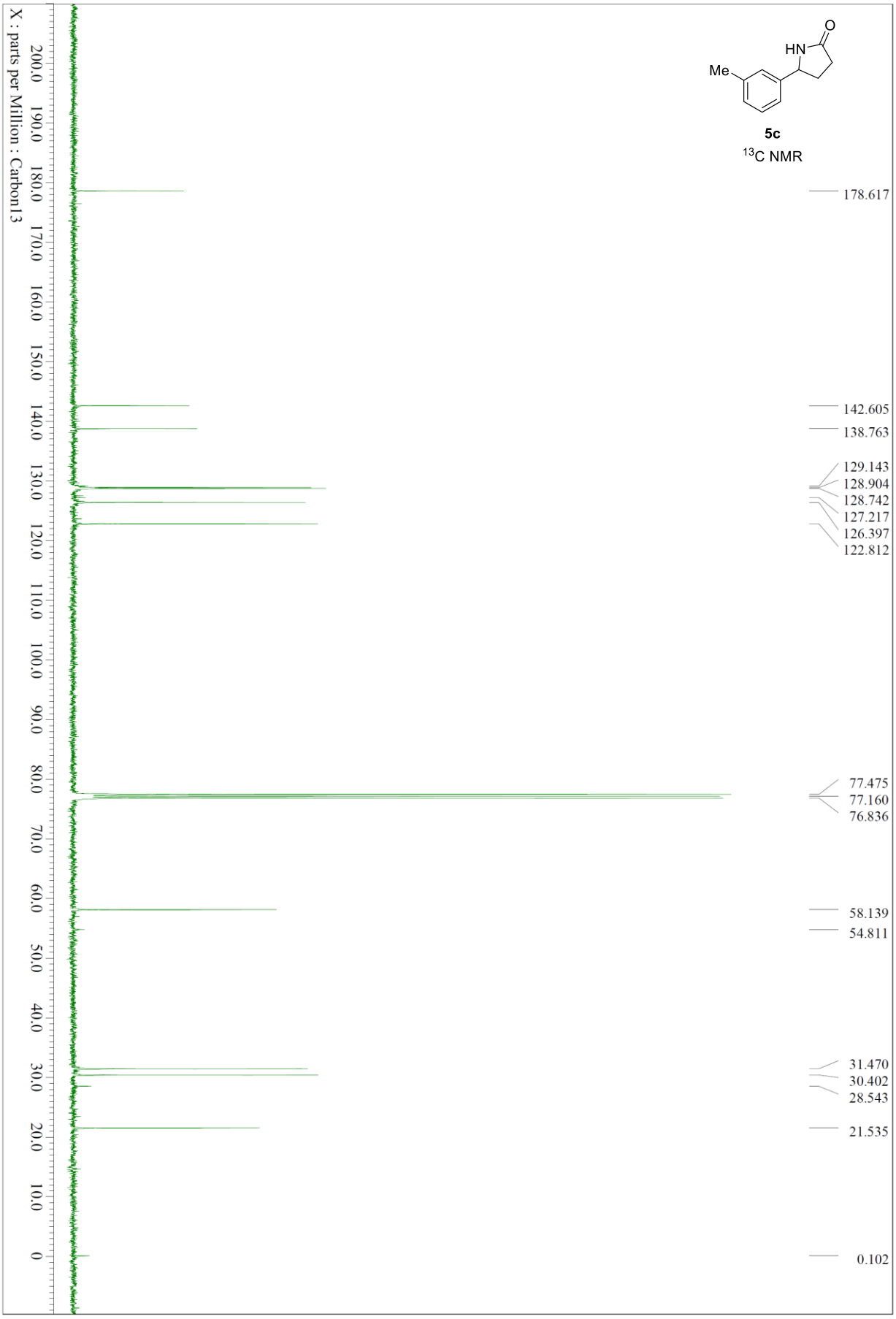
0.99
0.34
0.000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160.0
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140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
40.0
30.0
20.0
10.0
0
O
HN
Me
5c
13C NMR
178.617
142.605
138.763
129.143
128.904
128.742
127.217
126.397
122.812
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77.160
76.836
58.139
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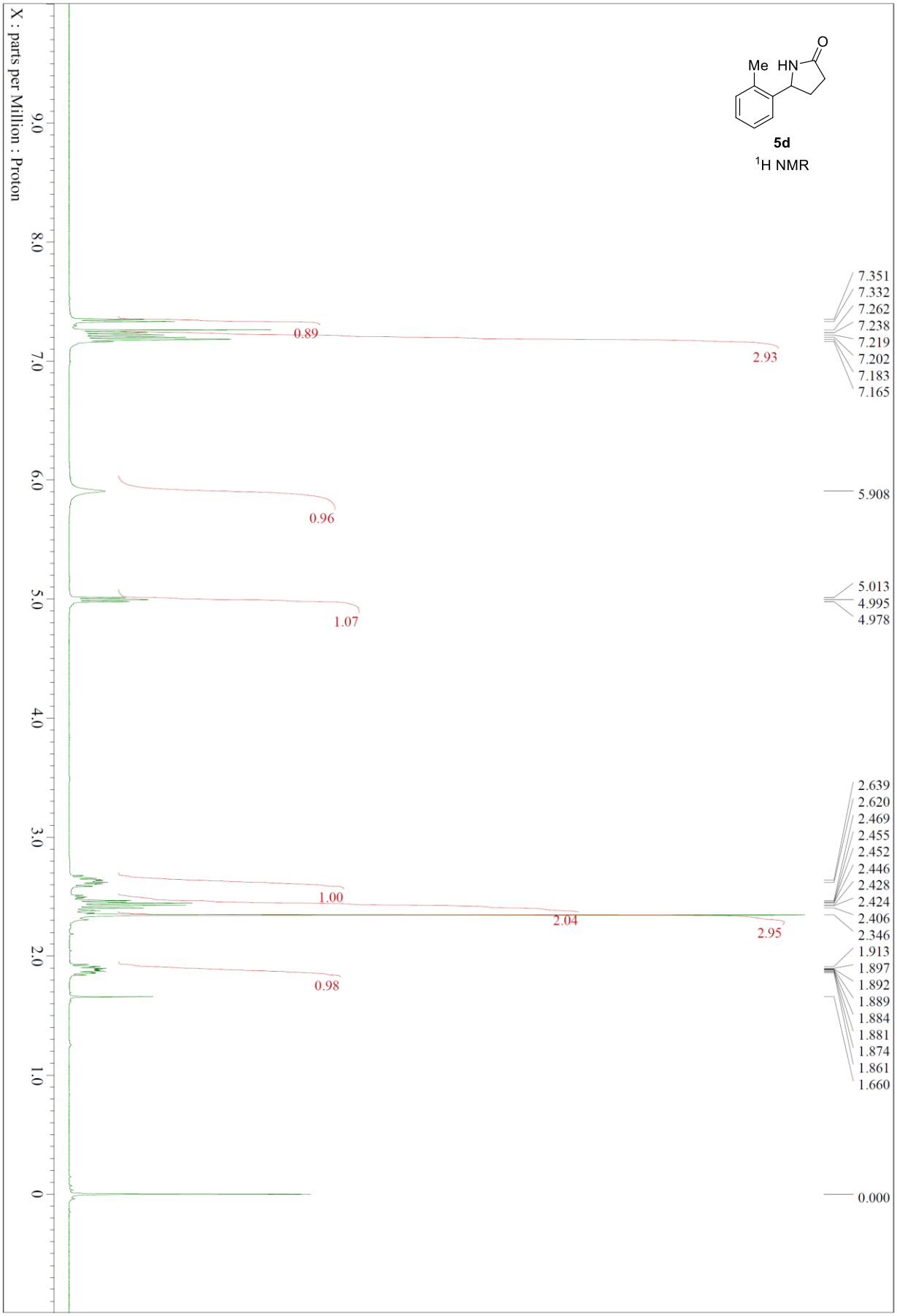
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5.0
4.0
3.0
2.0
1.0
0
Me
HN
O
5d
1H NMR
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7.332
7.262
7.238
7.219
7.202
7.183
7.165
5.908
5.013
4.995
4.978
2.639
2.620
2.469
2.455
2.452
2.446
2.428
2.424
2.406
2.346
1.913
1.897
1.892
1.889
1.884
1.881
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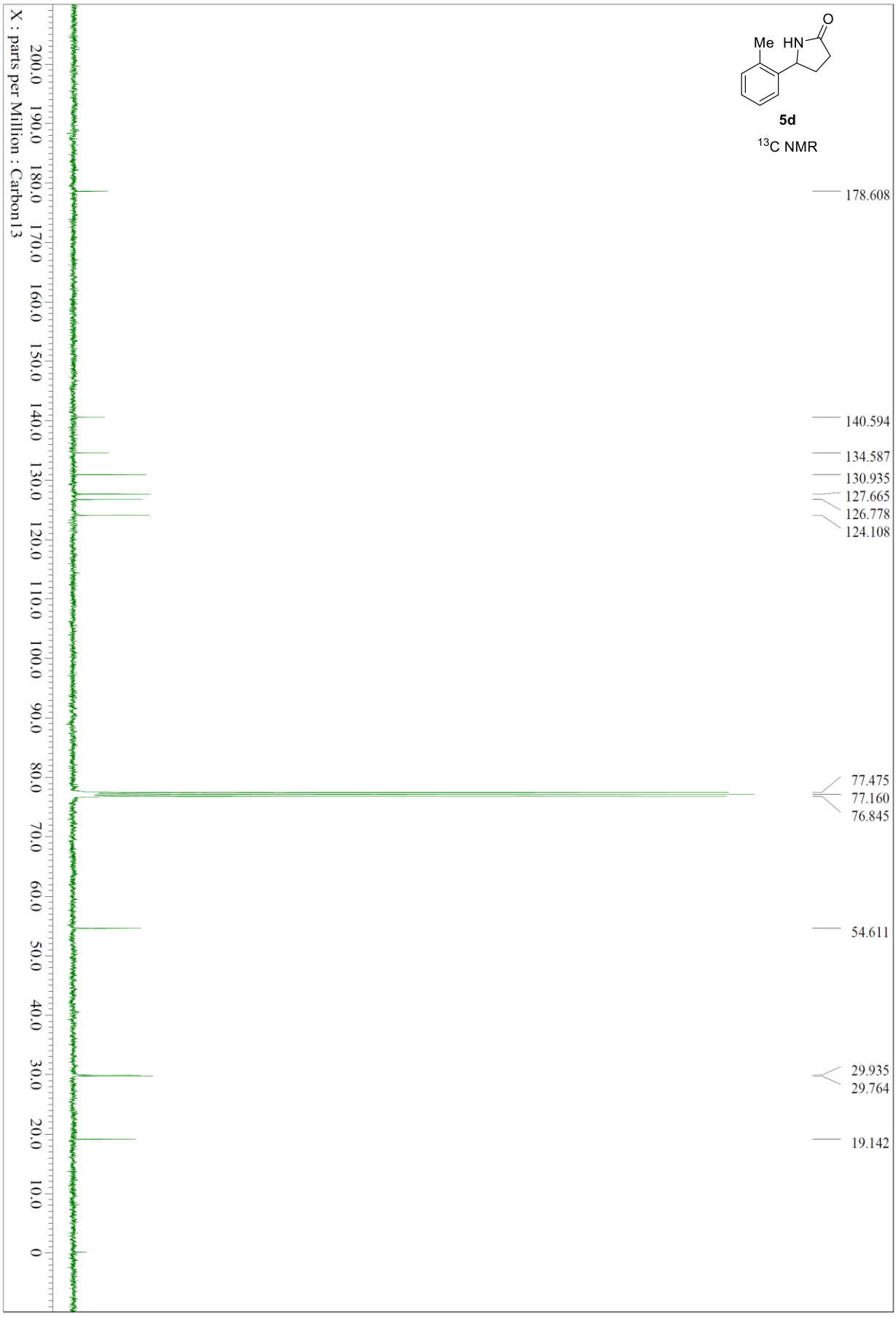
1.07
1.00
2.04
2.95
0.98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HN
O
5d
^{13}C NMR
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134.587
130.935
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126.778
124.108
77.475
77.160
76.845
54.611
29.935
29.764
19.142
X : parts per Million : Carbon13
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180.0
170.0
160.0
150.0
140.0
130.0
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90.0
80.0
70.0
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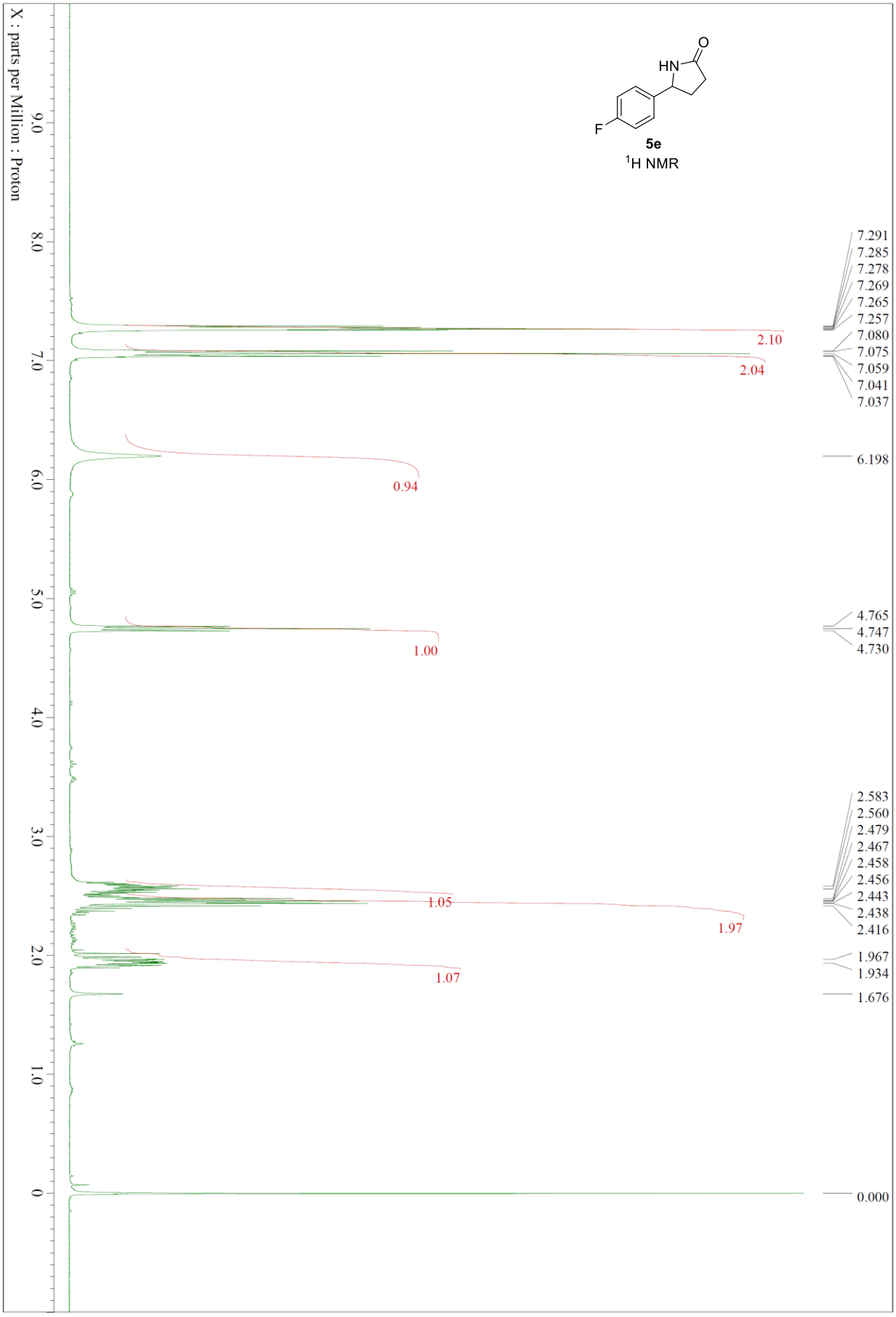
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5.0
4.0
3.0
2.0
1.0
0
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O
F
5e
1H NMR
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7.285
7.278
7.269
7.265
7.257
7.080
7.075
7.059
7.041
7.037
6.198
4.765
4.747
4.730
2.583
2.560
2.479
2.467
2.458
2.456
2.443
2.438
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0.94
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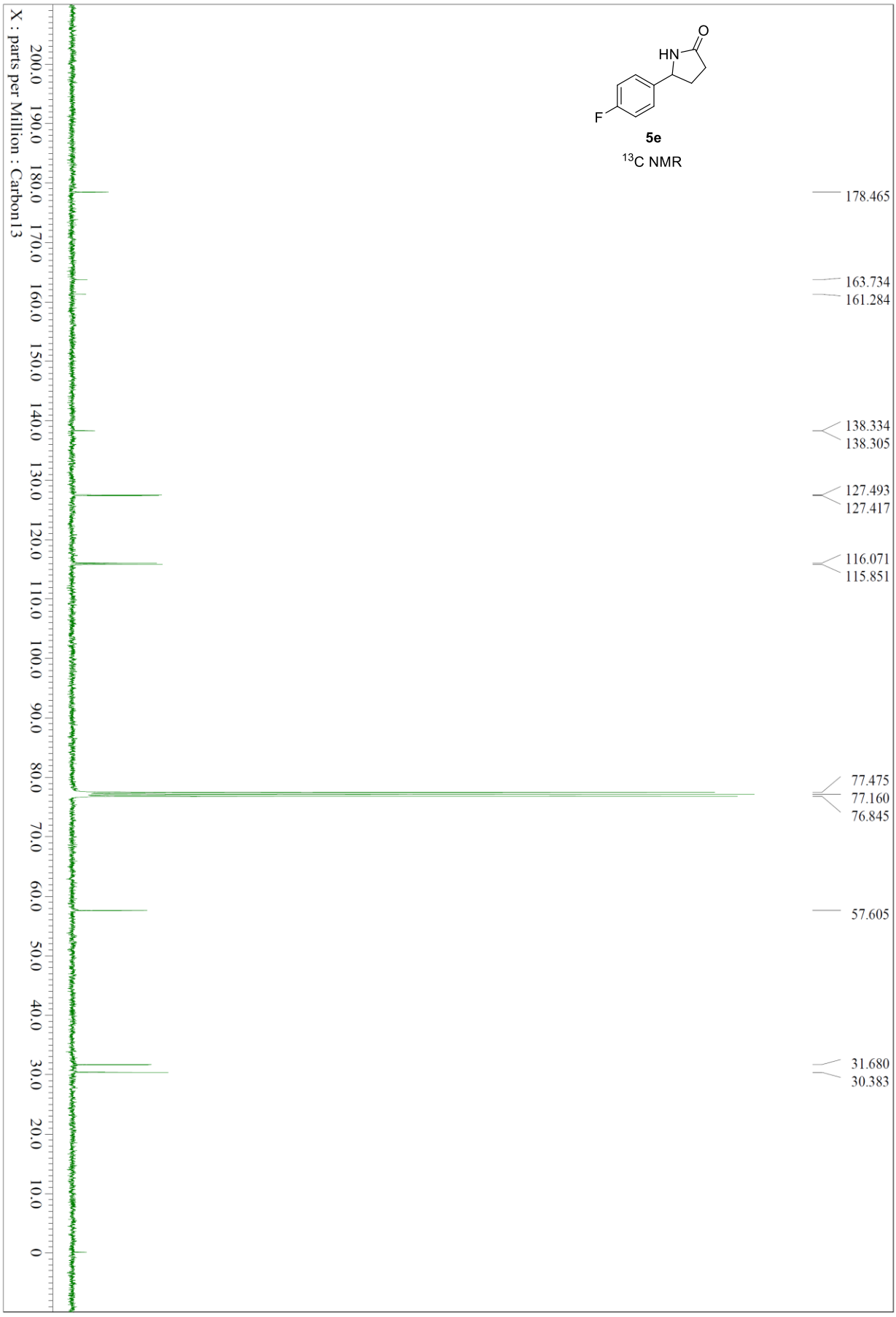
1.07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130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
40.0
30.0
20.0
10.0
0
HN
O
F
5e
13C NMR
178.465
163.734
161.284
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115.851
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77.160
76.845
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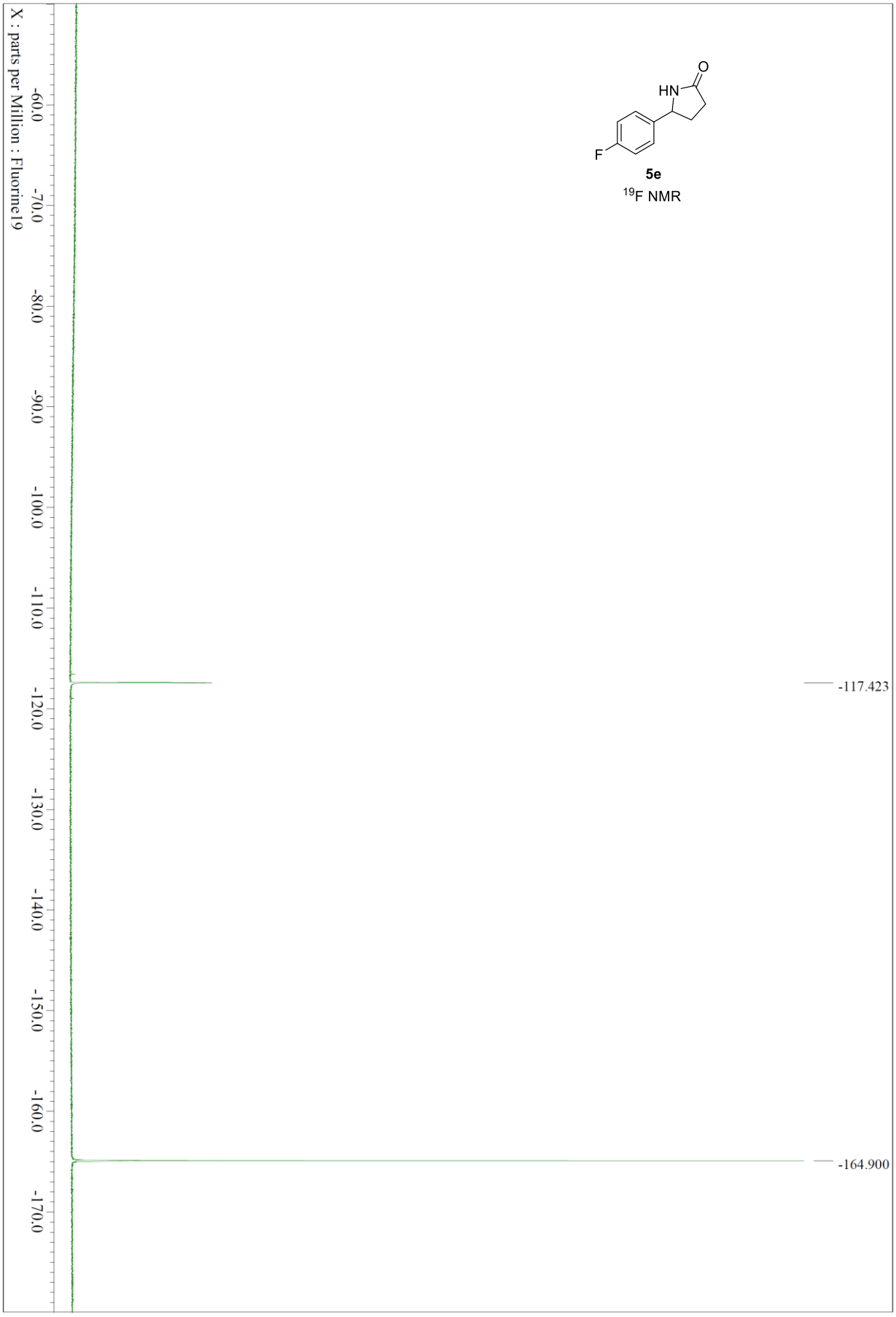
31.680
30.383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-160.0
-170.0
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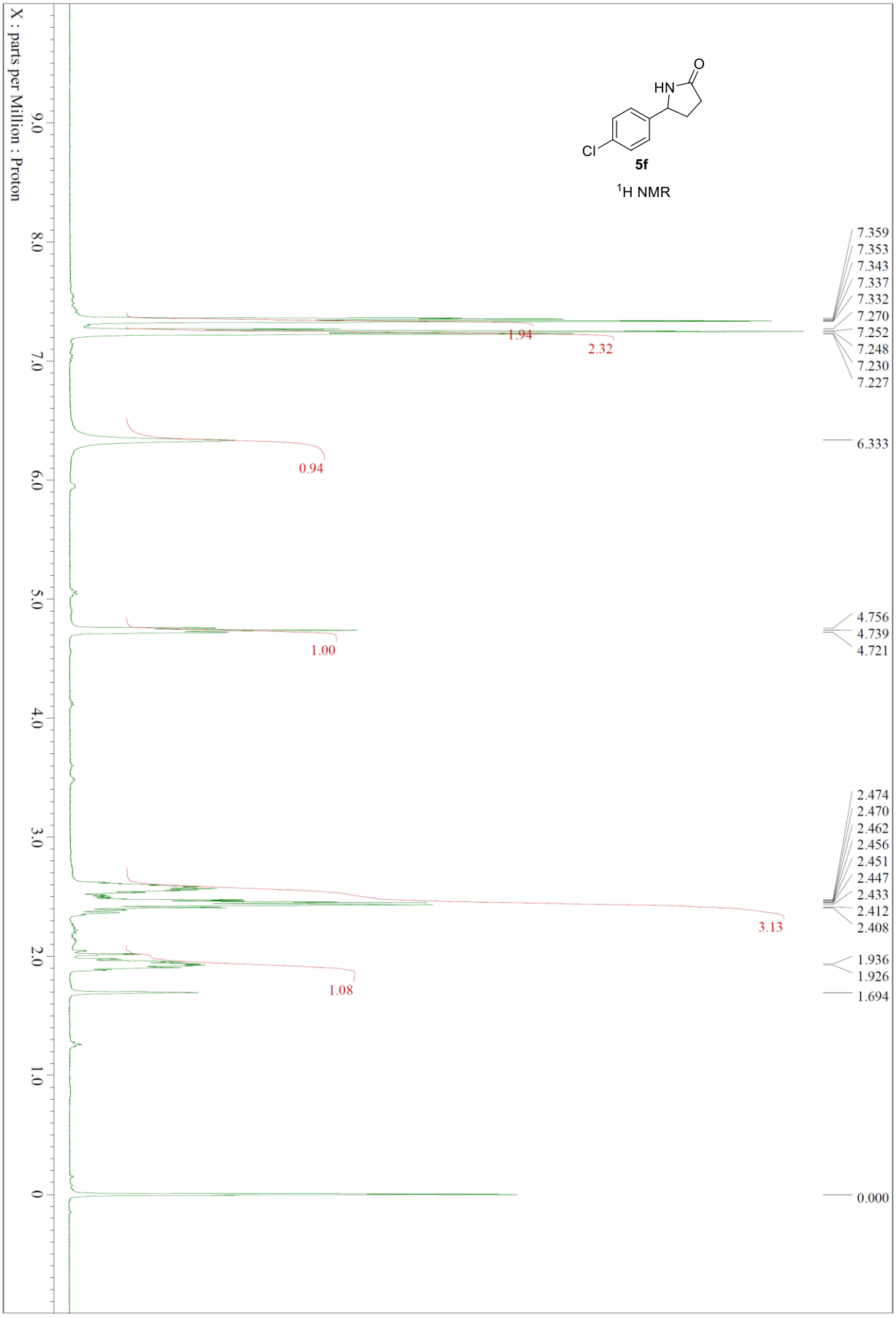
-164.900
HN
O
F

5e

^{19}F NMR


X : parts per Million : Proton
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4.0
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0
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O
Cl
5f
1H NMR
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7.343
7.337
7.332
7.270
7.252
7.248
7.230
7.227
6.333
4.756
4.739
4.721
2.474
2.470
2.462
2.456
2.451
2.447
2.433
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2.32
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1.00
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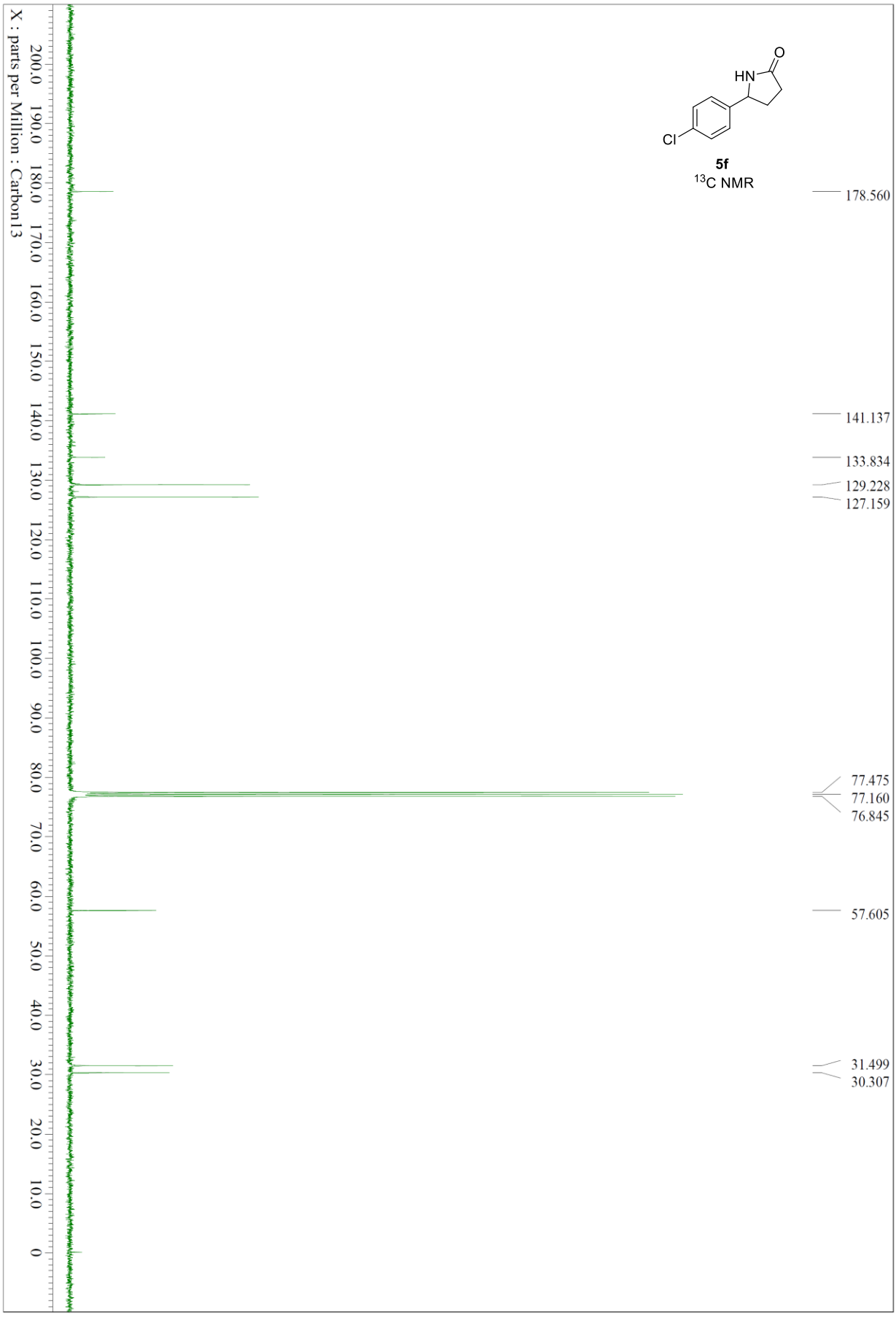
1.08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110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
HN
O
Cl
5f
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77.160
76.845
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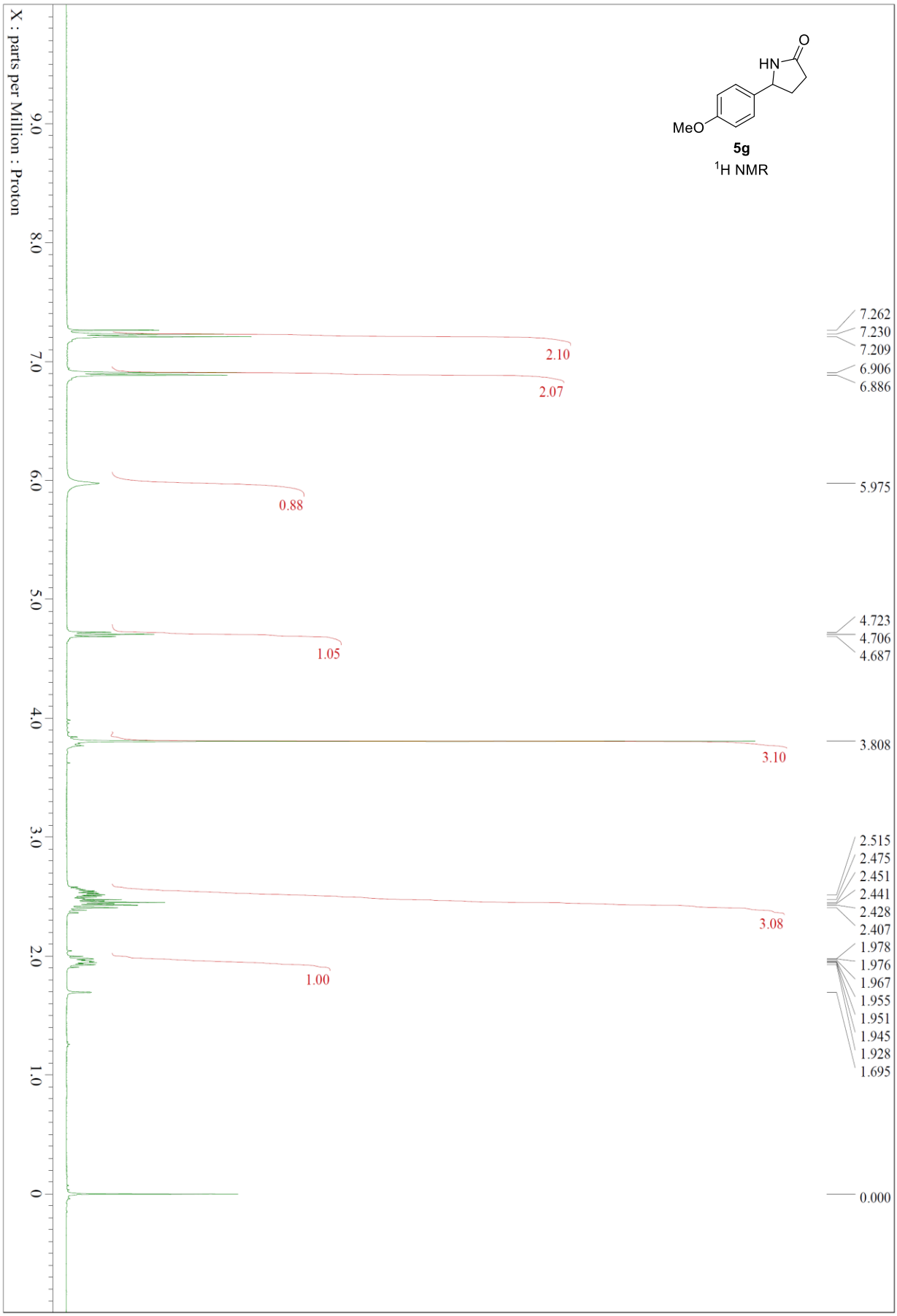
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1.0
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O
MeO
5g
1H NMR
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2.07
0.88
1.05
3.10
3.08
1.00
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7.230
7.209
6.906
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2.515
2.475
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2.441
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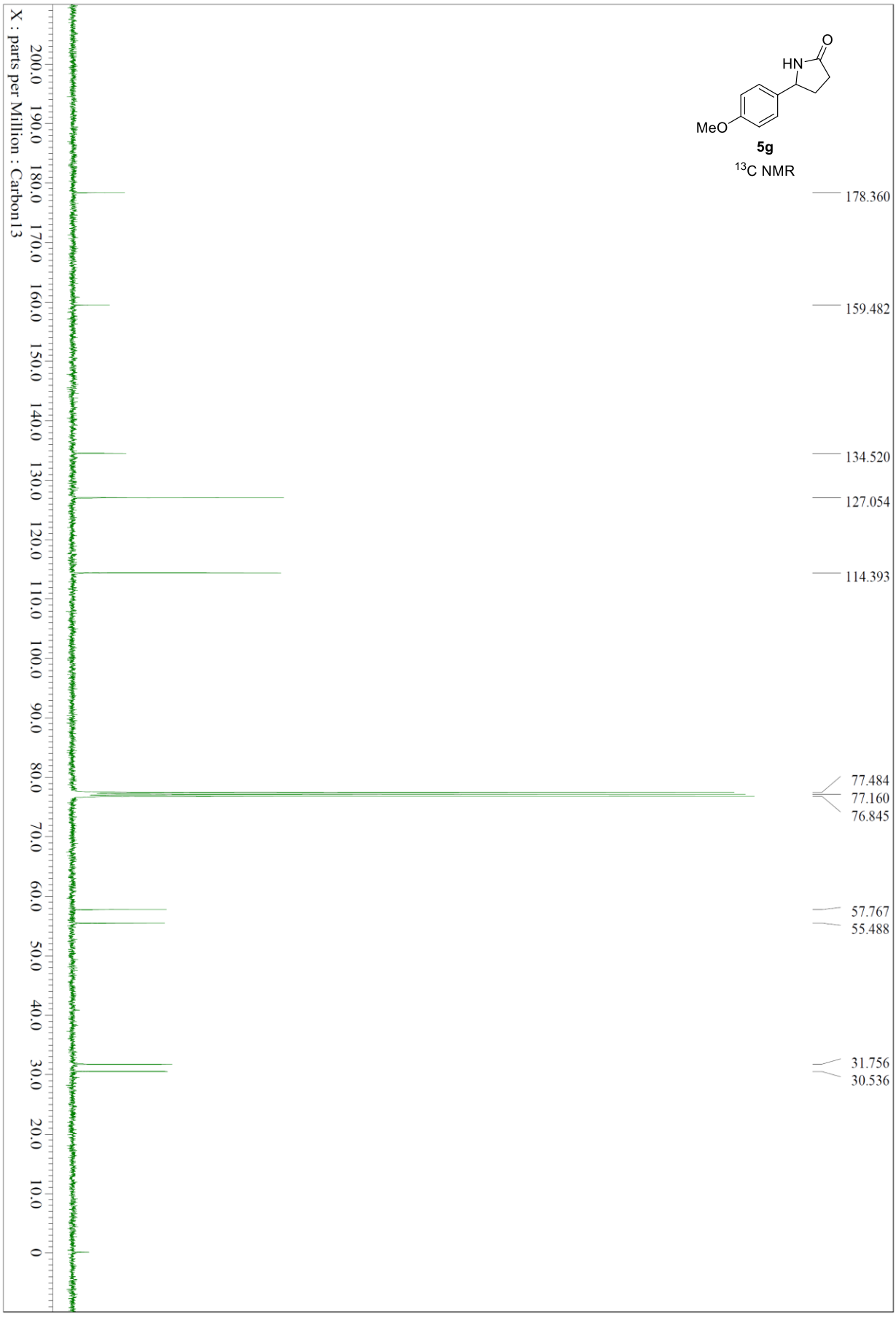
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120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
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O
MeO
5g
13C NMR
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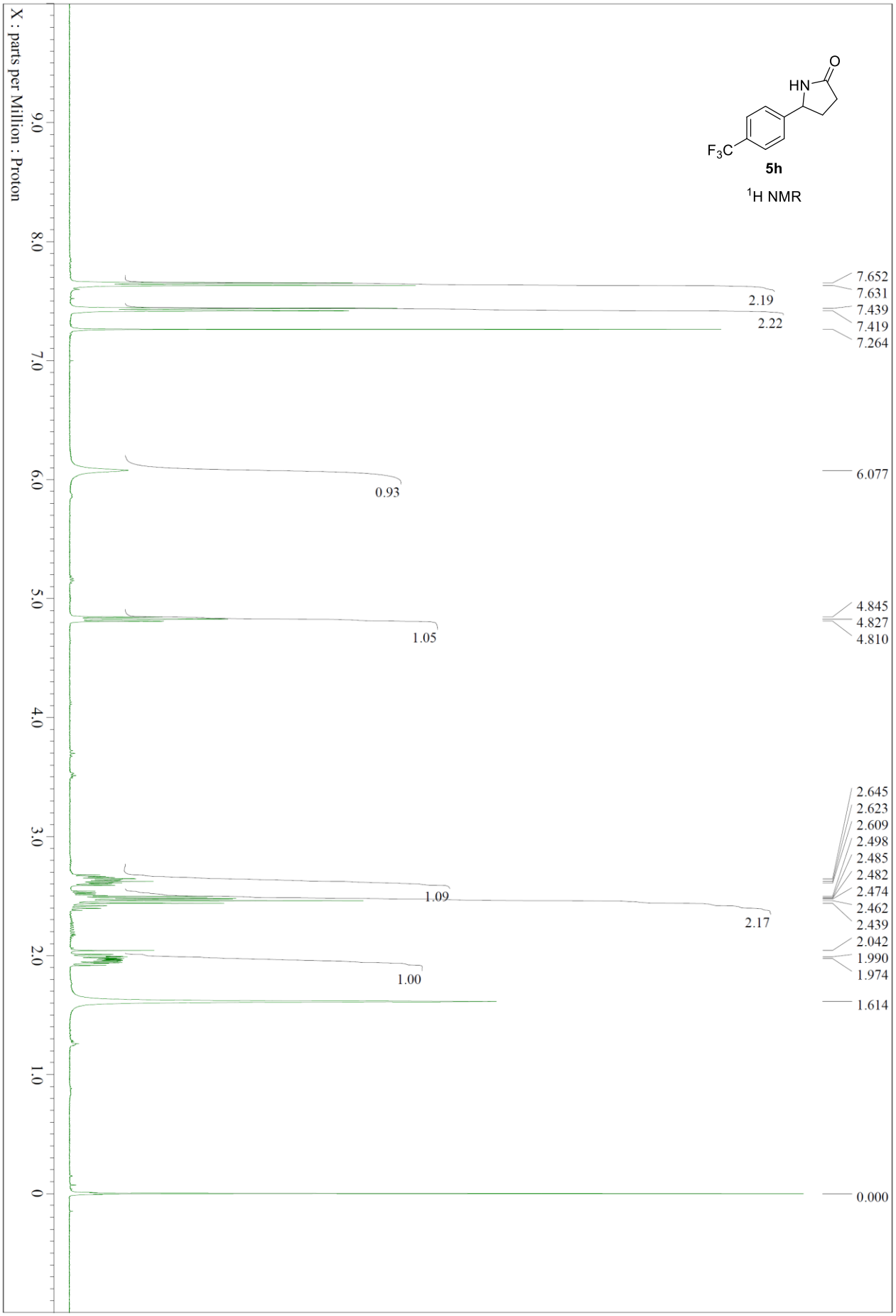
30.536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O
F3C
5h
1H NMR
7.652
7.631
7.439
7.419
7.264
2.19
2.22
6.077
0.93
4.845
4.827
4.810
1.05
2.645
2.623
2.609
2.498
2.485
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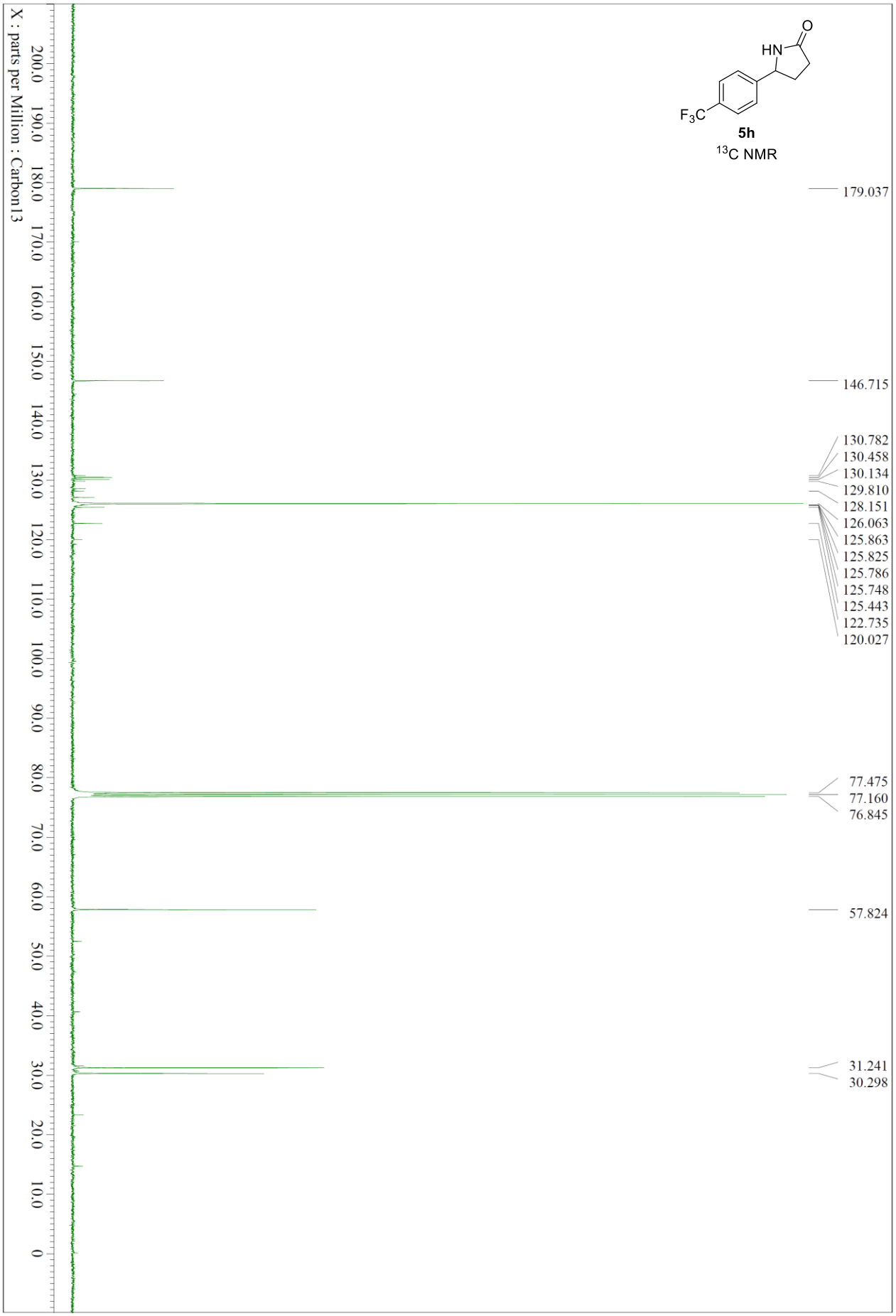
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130.0
120.0
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100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
HN
O
F3C
5h
13C NMR
179.037
146.715
130.782
130.458
130.134
129.810
128.151
126.063
125.863
125.825
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120.027
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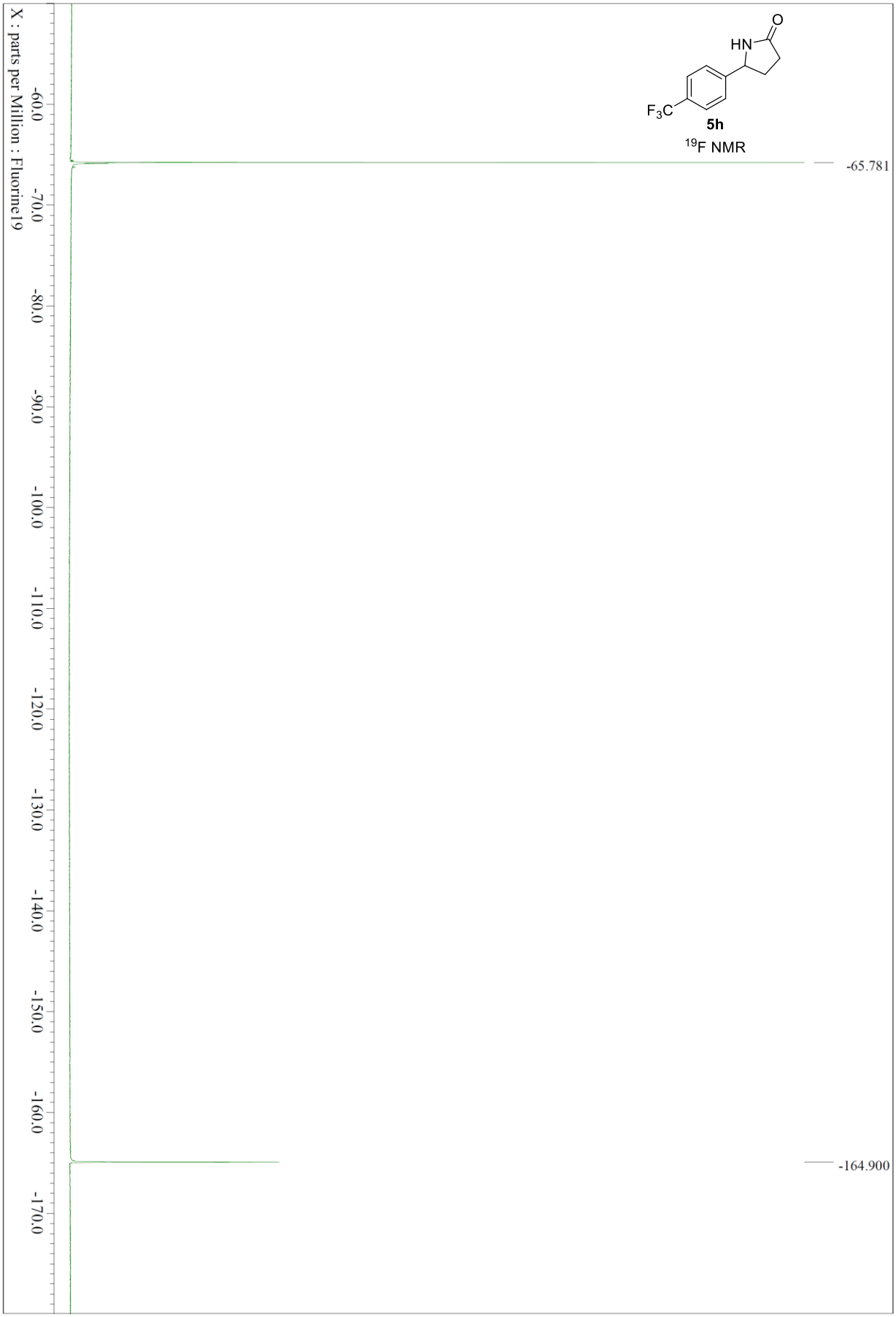
X : parts per Million : Fluorine19
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-80.0
-90.0
-100.0
-110.0
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-160.0
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O
F3C
5h
19F NMR
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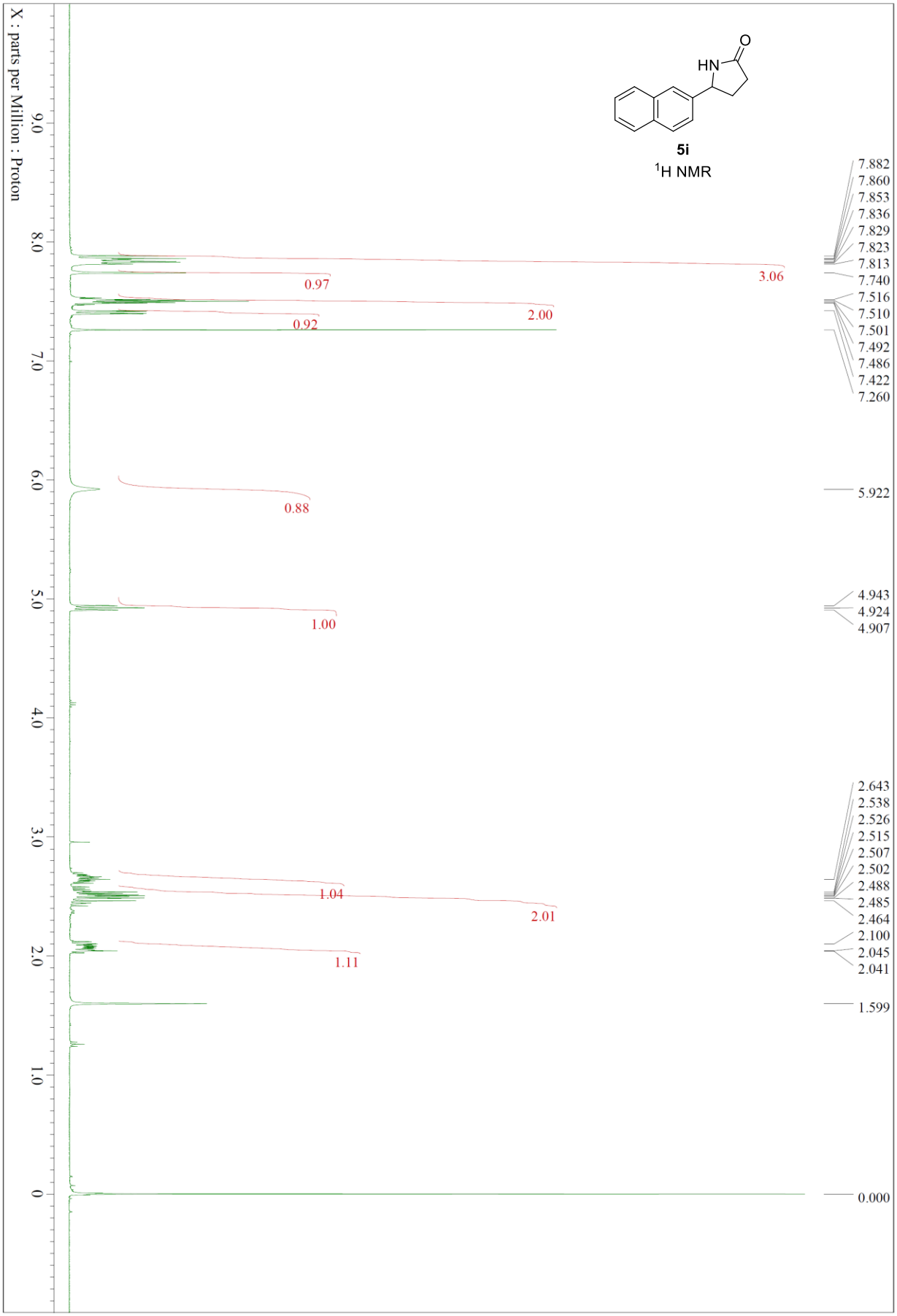
-164.900


X : parts per Million : Proton
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1.0
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O
5i
1H NMR
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7.836
7.829
7.823
7.813
7.740
7.516
7.510
7.501
7.492
7.486
7.422
7.260
5.922
4.943
4.924
4.907
2.643
2.538
2.526
2.515
2.507
2.502
2.488
2.485
2.464
2.100
2.045
2.041
1.599
0.000
3.06
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2.00
0.92
0.88
1.00
1.04
2.01
1.11


X : parts per Million : Carbon13
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180.0
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120.0
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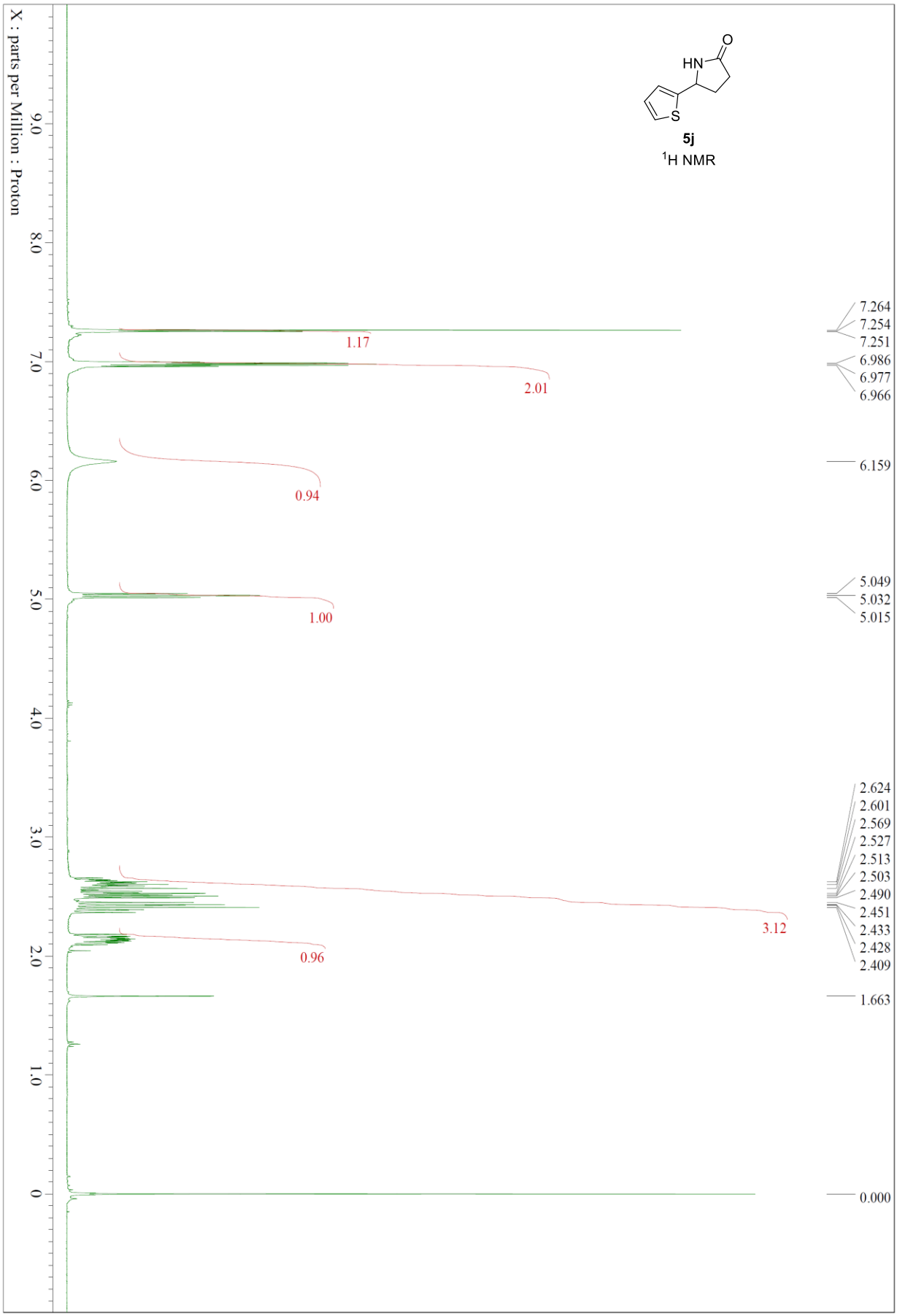
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
HN
O
5i
13C NMR
178.827
139.926
133.328
133.061
129.038
127.922
127.798
126.587
126.215
124.385
123.717
77.475
77.160
76.845
58.253
31.184
30.355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O
S
5j
1H NMR
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2.01
0.94
1.00
3.12
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7.264
7.254
7.251
6.986
6.977
6.966
6.159
5.049
5.032
5.015
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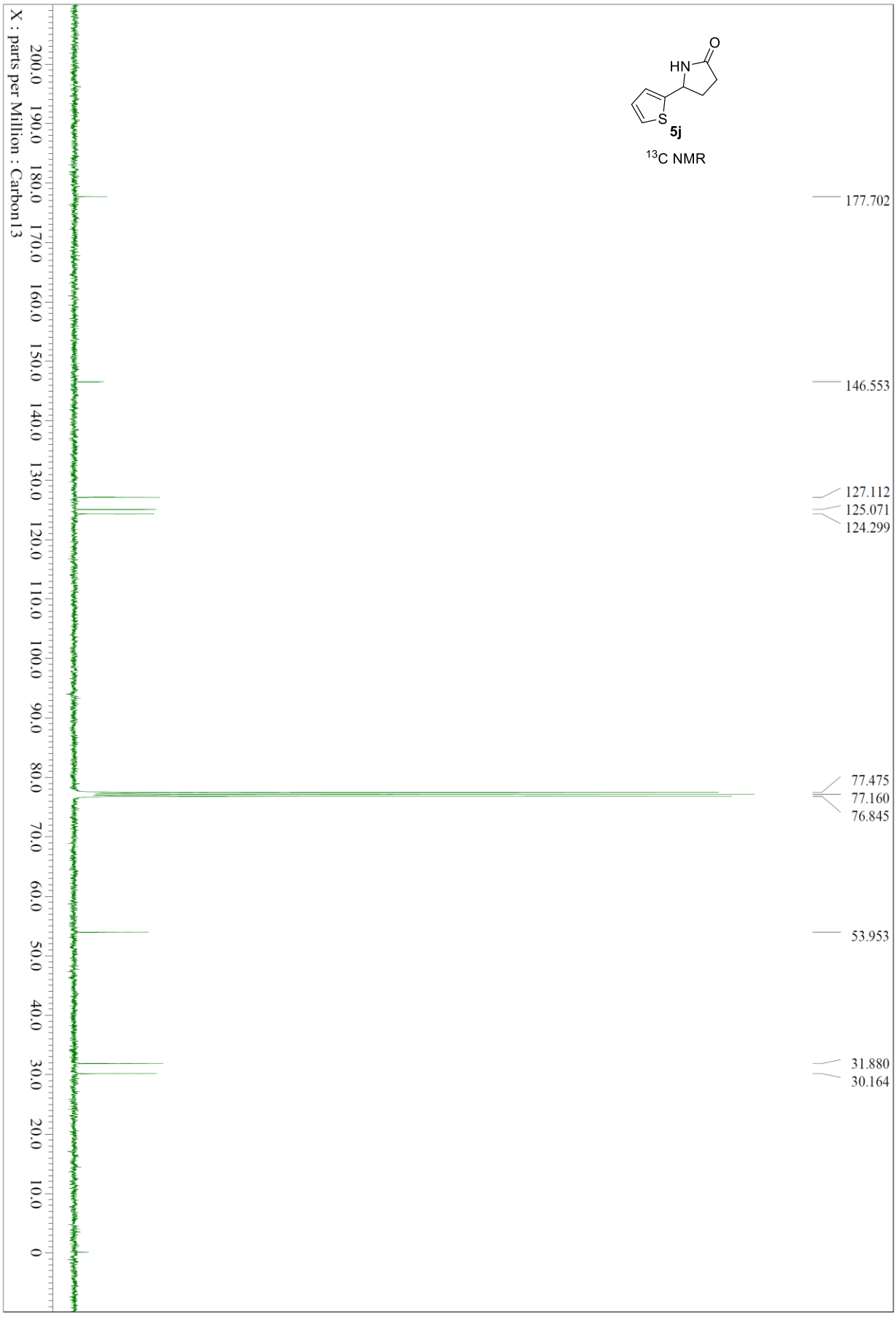
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80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
HN
O
S
5j
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76.845
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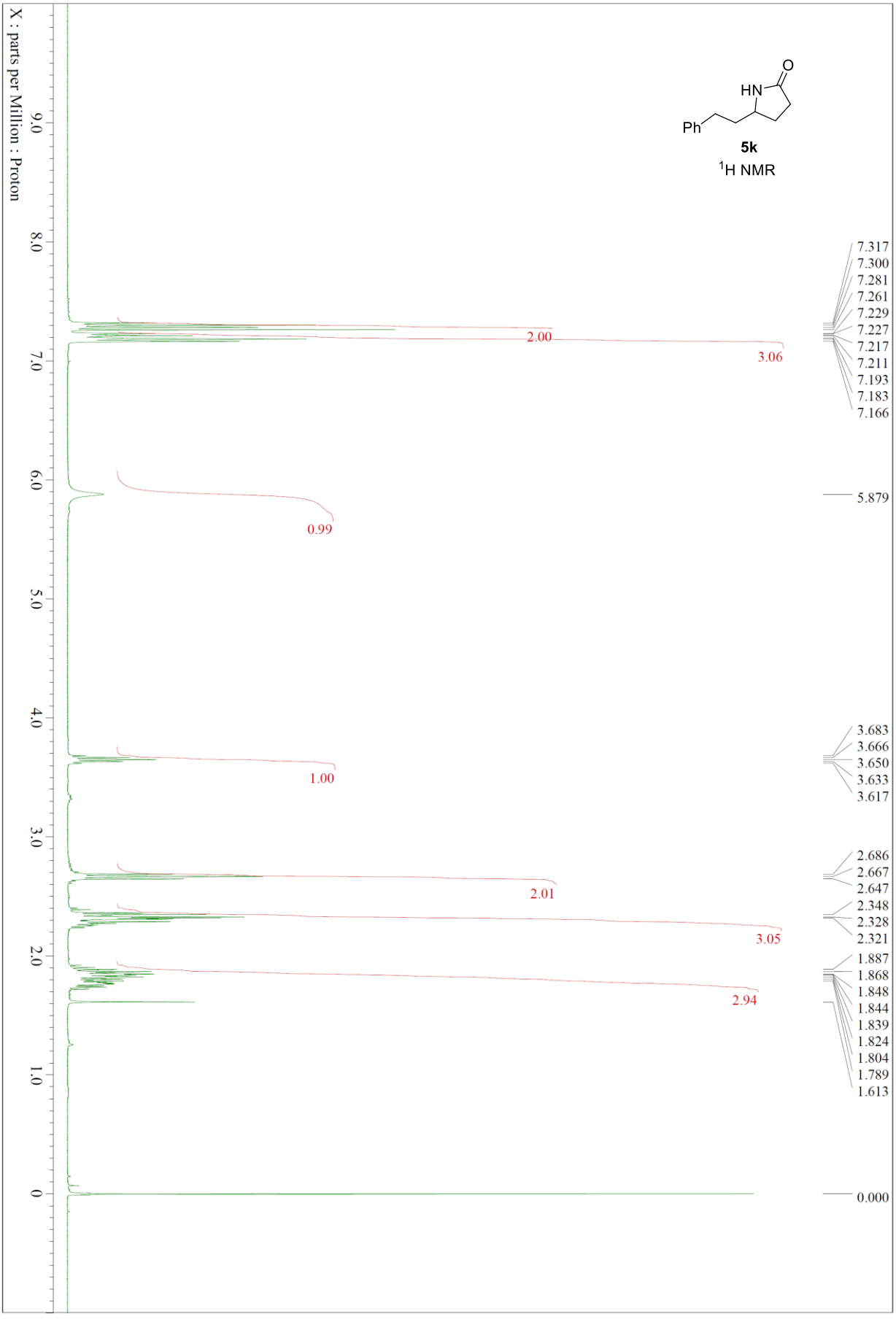
30.164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Ph
5k
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7.261
7.229
7.227
7.217
7.211
7.193
7.183
7.166
5.879
3.683
3.666
3.650
3.633
3.617
2.686
2.667
2.647
2.348
2.328
2.321
1.887
1.868
1.848
1.844
1.839
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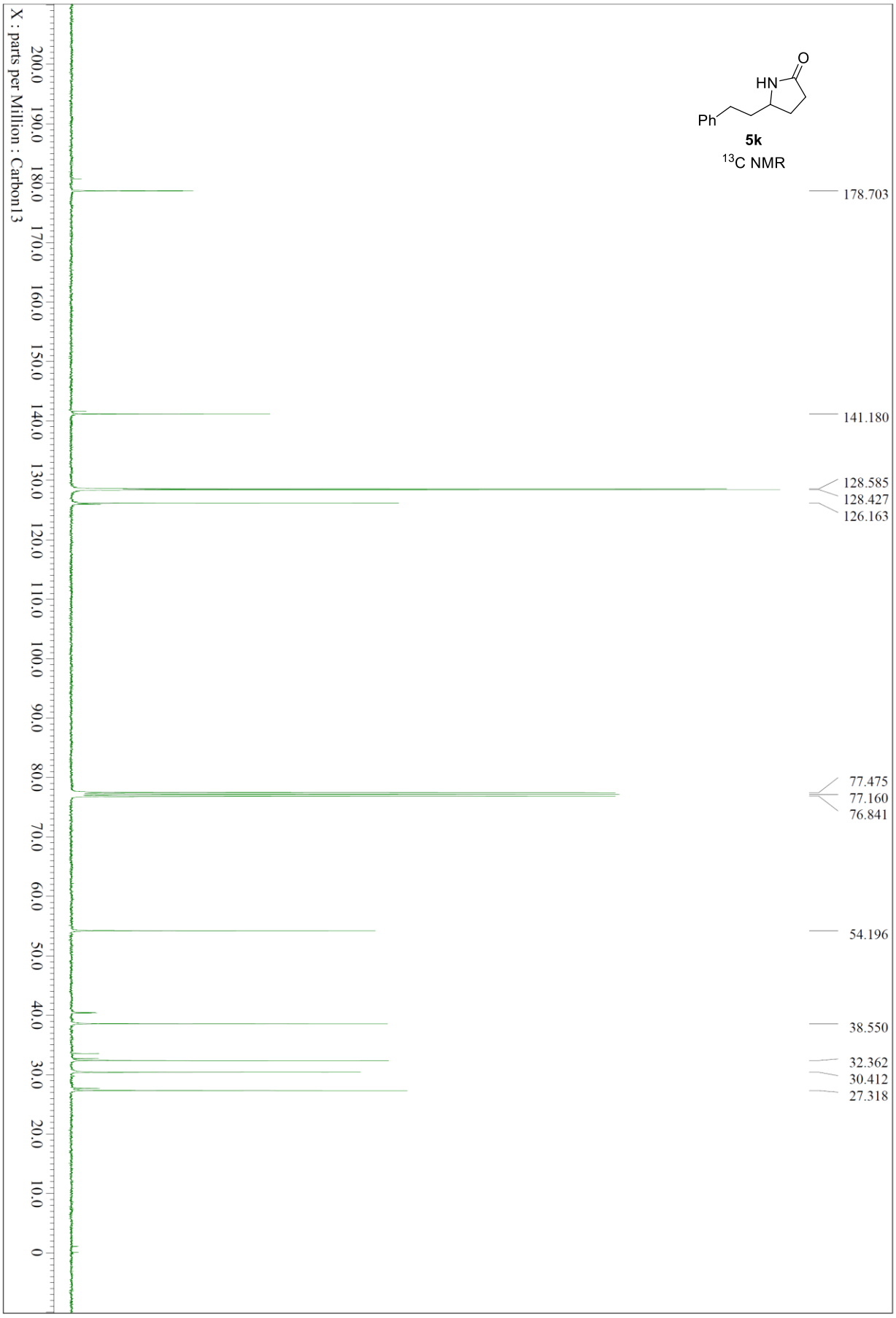
3.05
2.94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10.0
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Ph
5k
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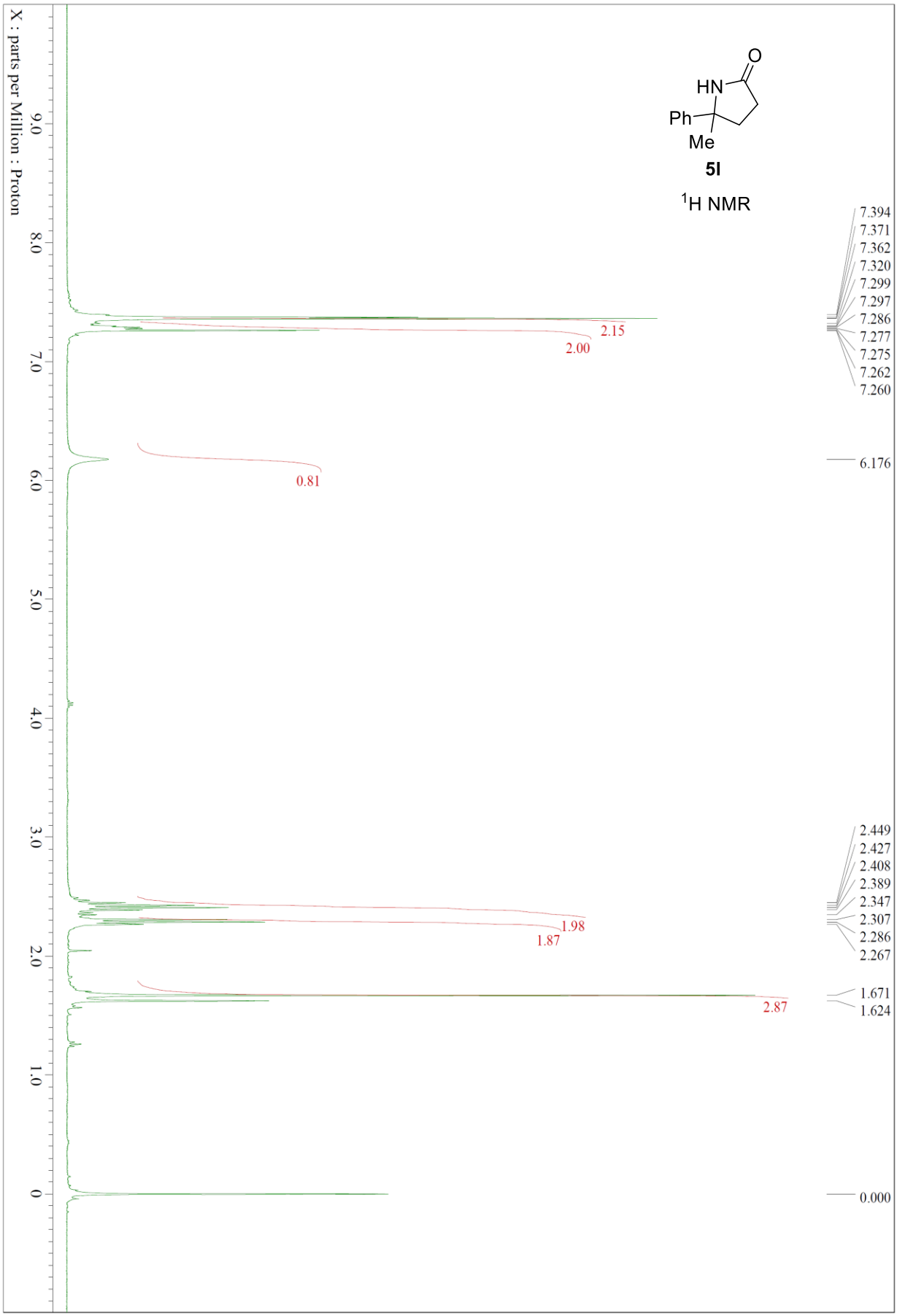
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Ph
Me
5l
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7.371
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7.320
7.299
7.297
7.286
7.277
7.275
7.262
7.260
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2.427
2.408
2.389
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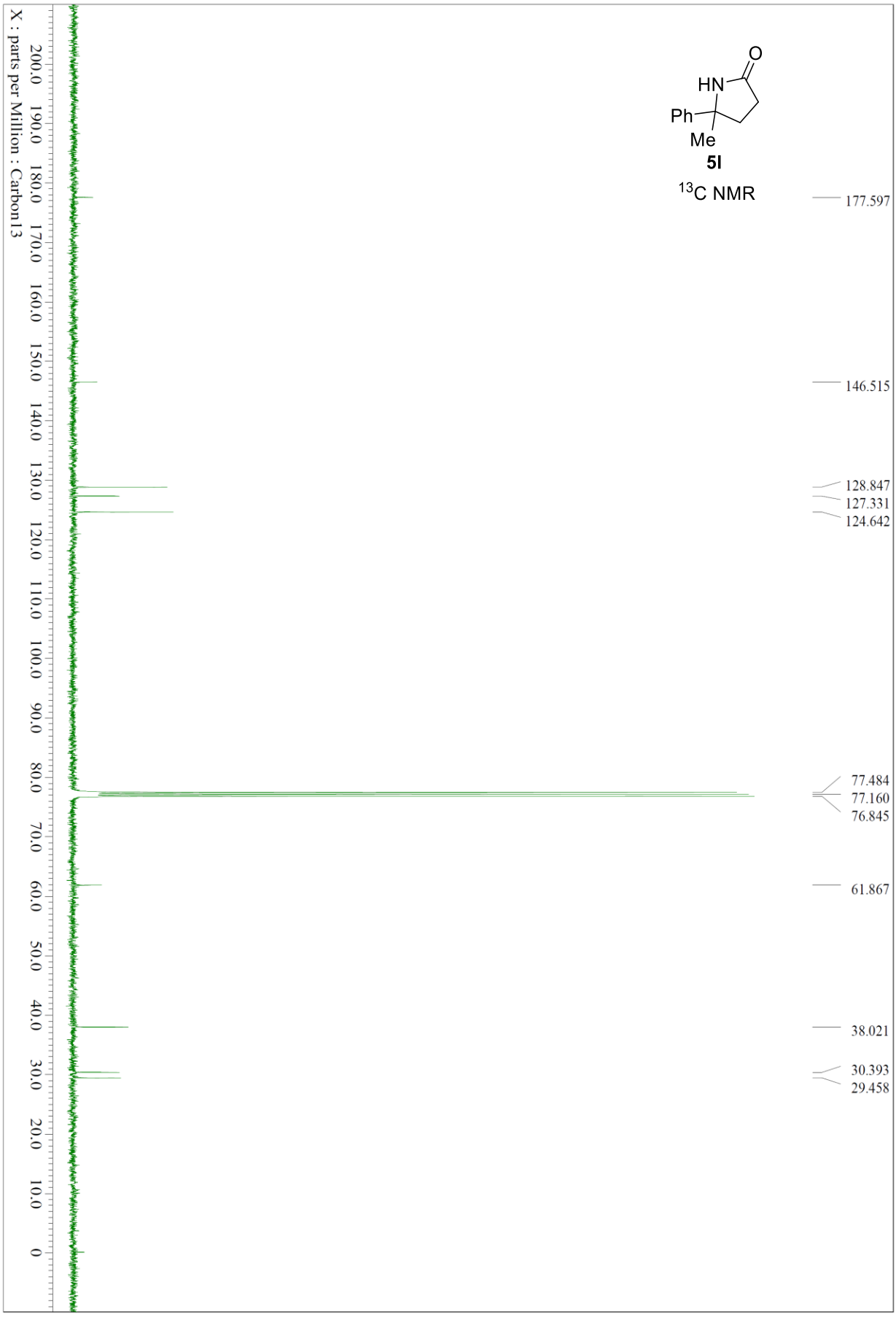
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80.0
70.0
60.0
50.0
40.0
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20.0
10.0
0
O
HN
Ph
Me
5l
13C NMR
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76.845
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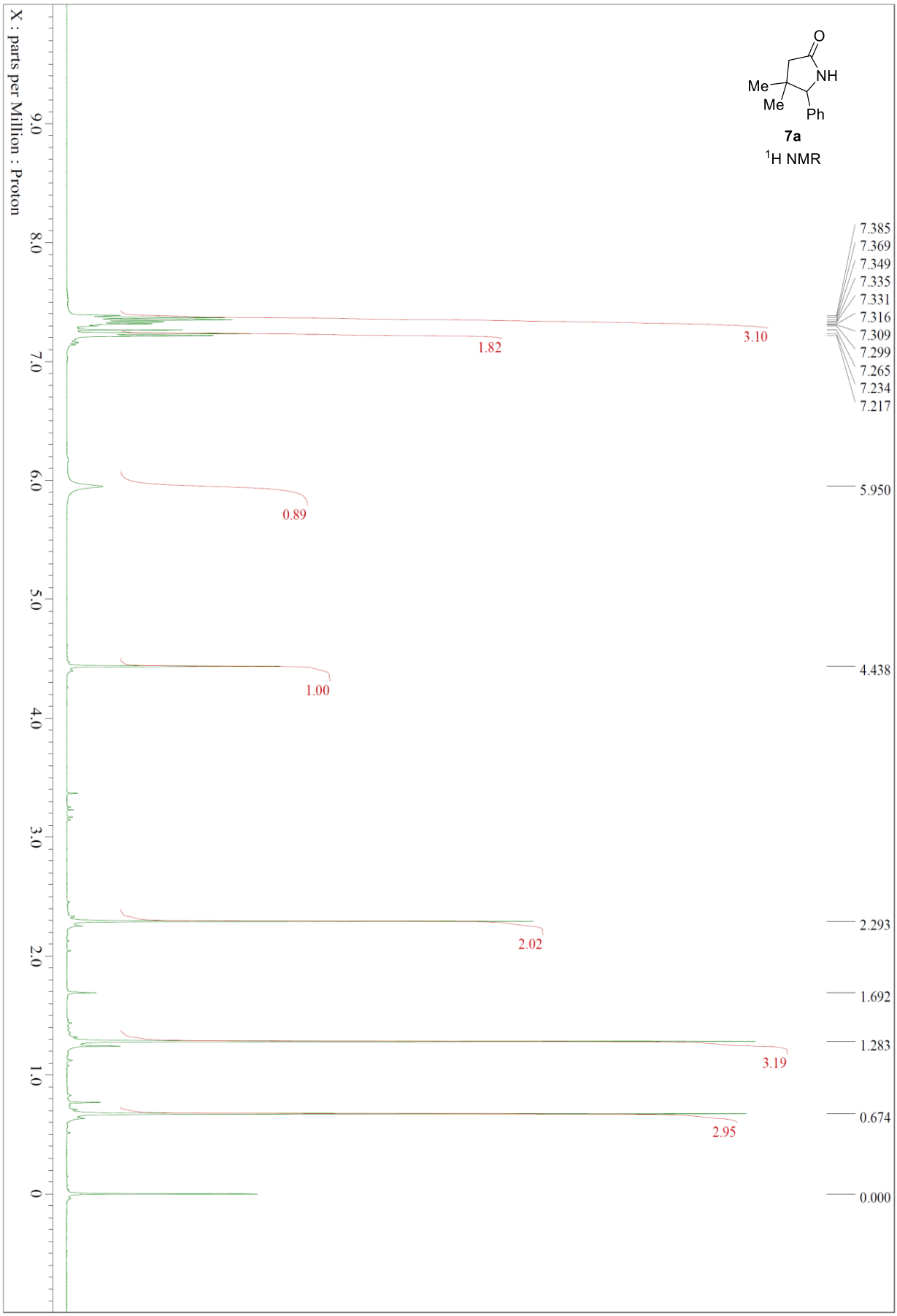
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1.0
0
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NH
Me
Me
Ph
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1H NMR
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7.349
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7.309
7.299
7.265
7.234
7.217
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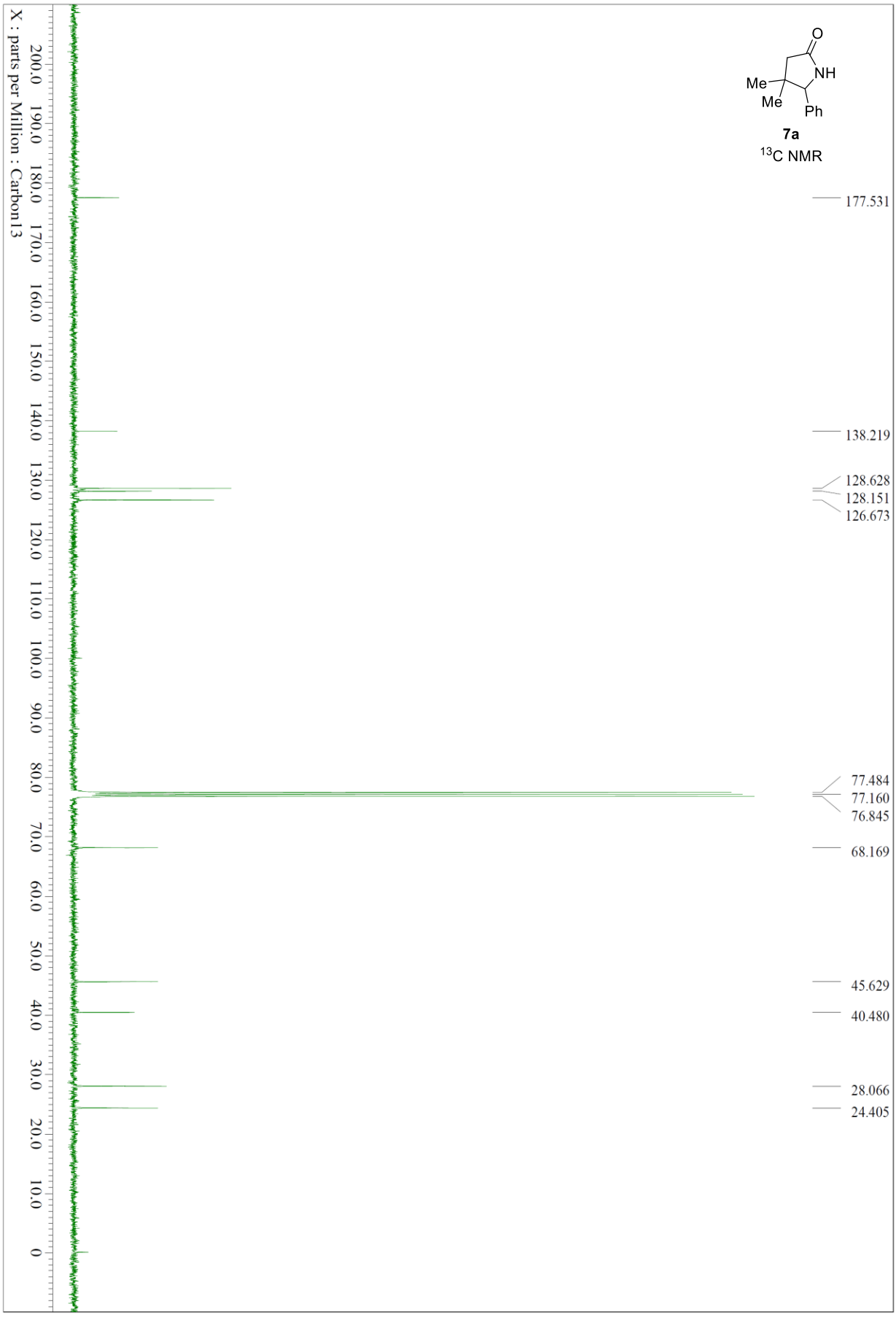
2.95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80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
O
NH
Me
Me
Ph
7a
13C NMR
177.531
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126.673
77.484
77.160
76.845
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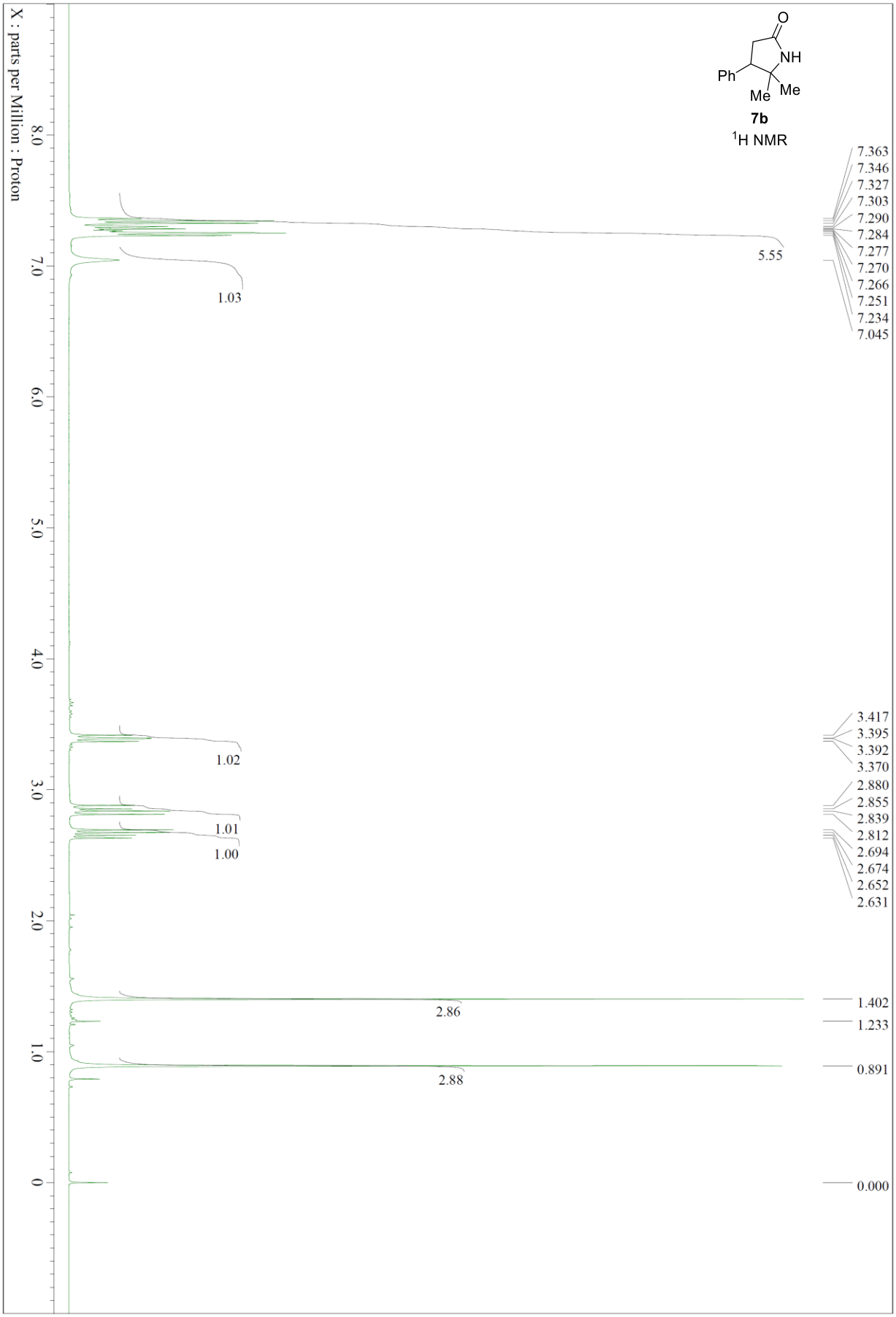
24.405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4.0
3.0
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0
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NH
Ph
Me
Me
7b
1H NMR
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7.346
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7.303
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7.284
7.277
7.270
7.266
7.251
7.234
7.045
5.55
1.03
1.02
1.01
1.00
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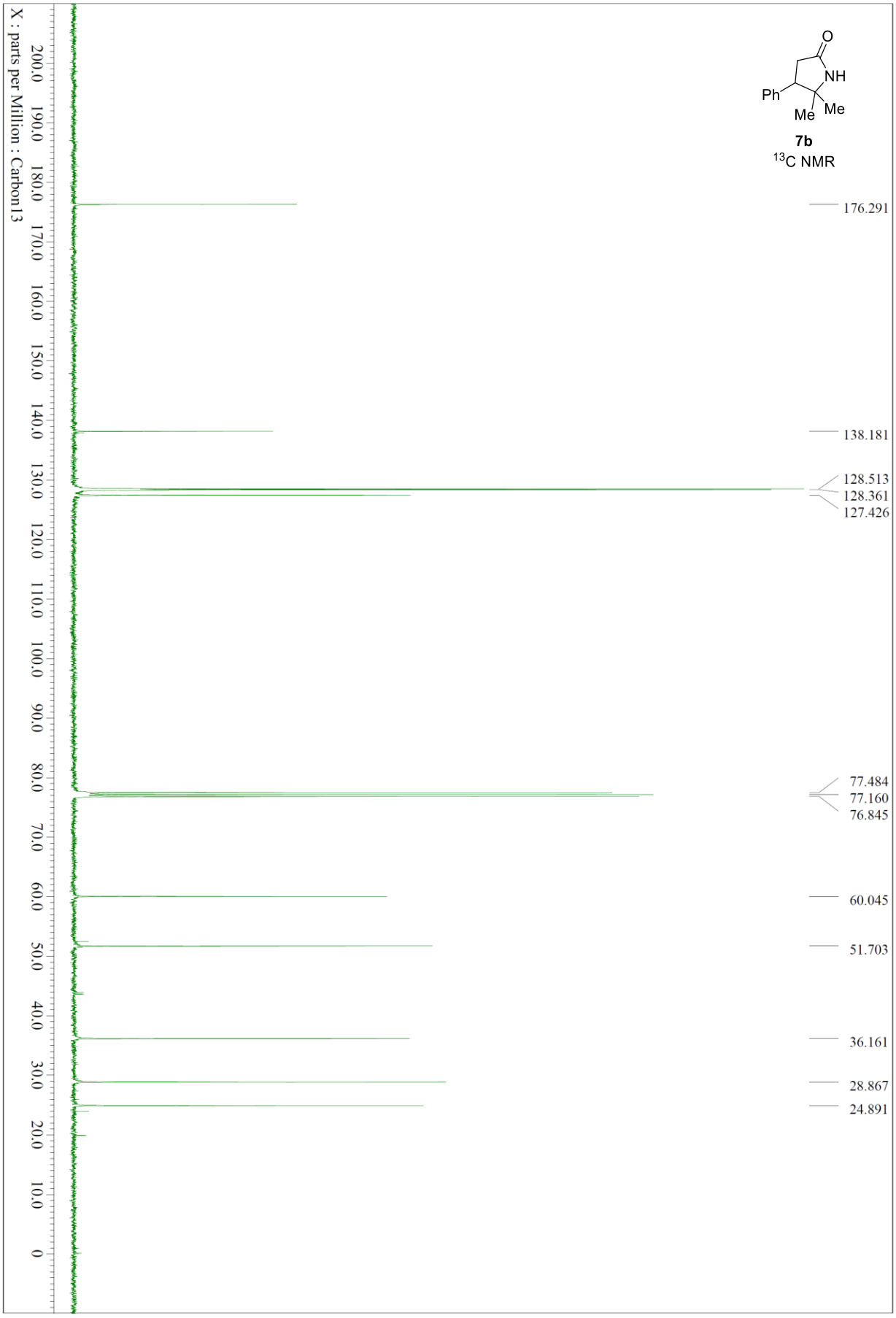
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NH
Ph
Me
Me
7b
13C NMR
176.291
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77.160
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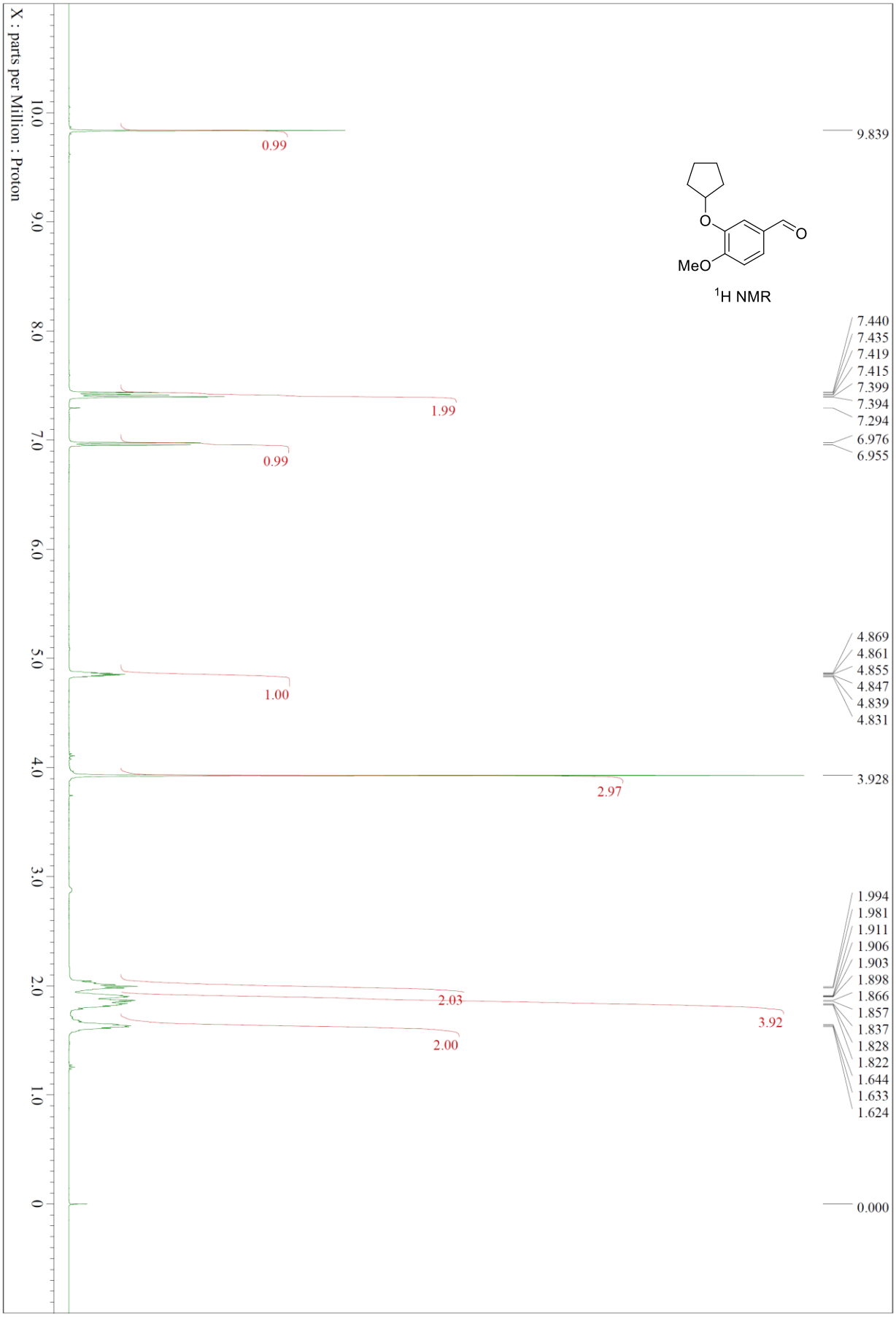
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0
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1.99
0.99
1.00
2.97
2.03
3.92
2.00
O
O
MeO
1H NMR
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7.440
7.435
7.419
7.415
7.399
7.394
7.294
6.976
6.955
4.869
4.861
4.855
4.847
4.839
4.831
3.928
1.994
1.981
1.911
1.906
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1.866
1.857
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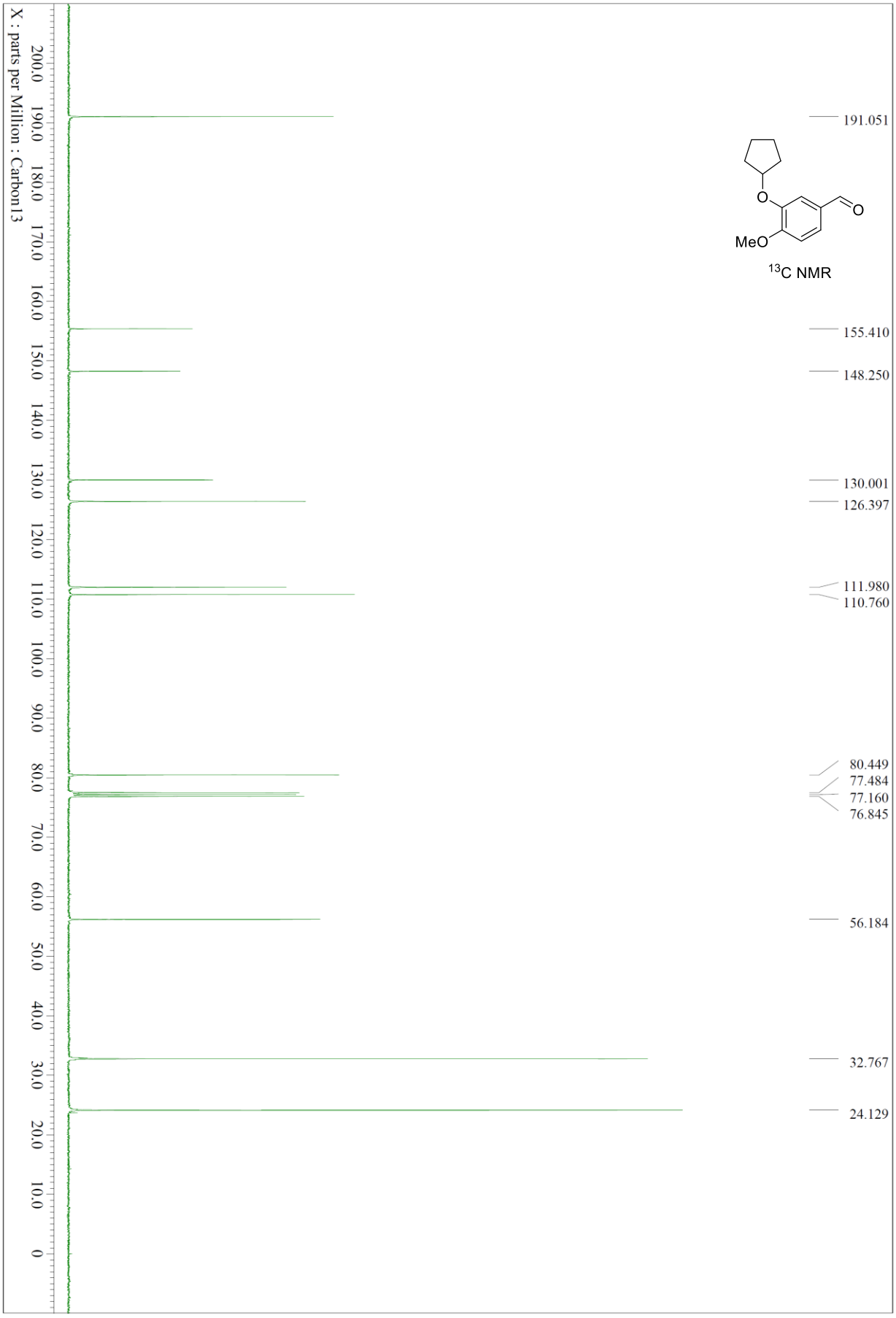
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90.0
80.0
70.0
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20.0
10.0
0
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155.410
148.250
130.001
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76.845
56.184
32.767
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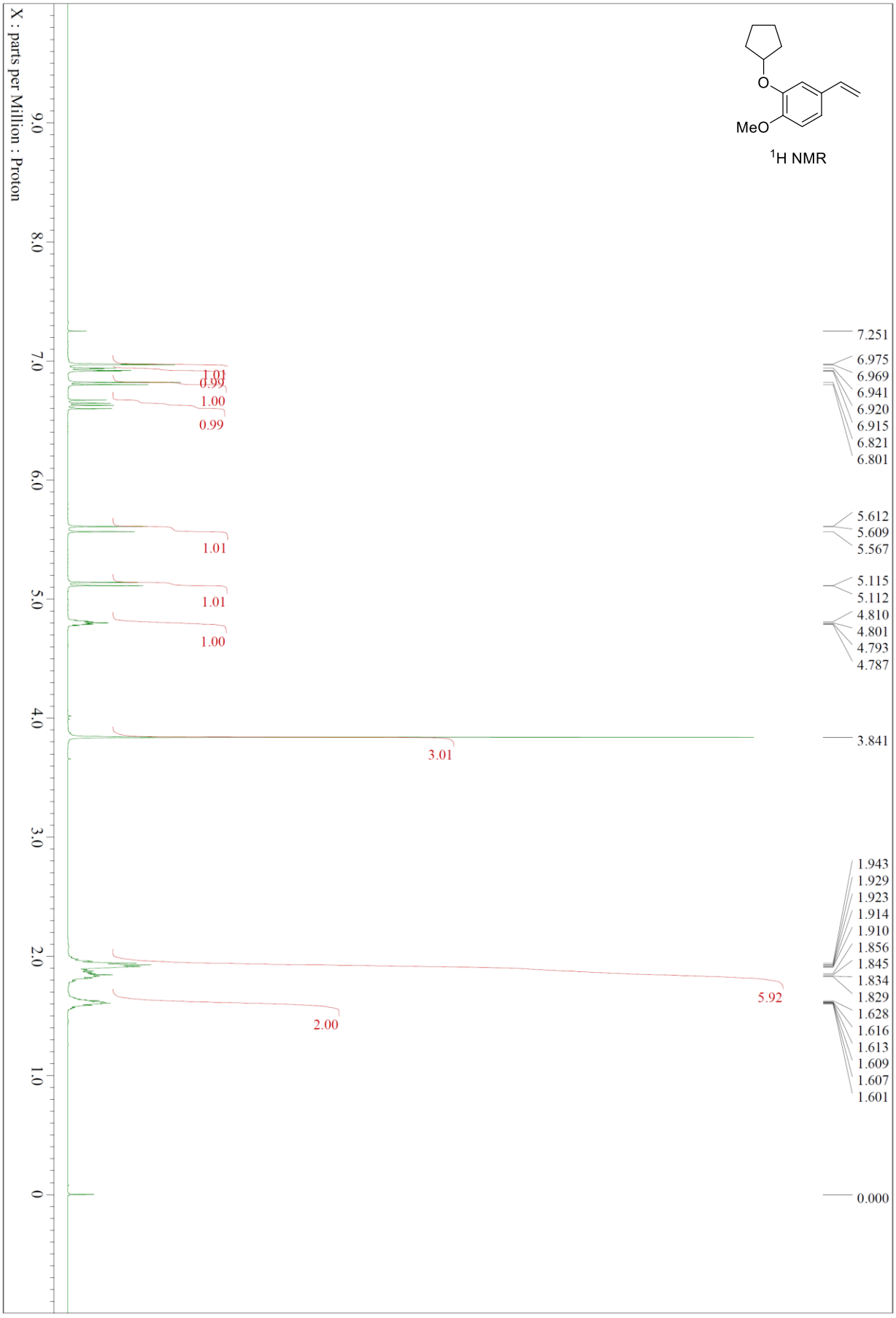
O
MeO
13C NMR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0
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MeO
1H NMR
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0.99
1.00
0.99
1.01
1.01
1.00
3.01
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6.941
6.920
6.915
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6.801
5.612
5.609
5.567
5.115
5.112
4.810
4.801
4.793
4.787
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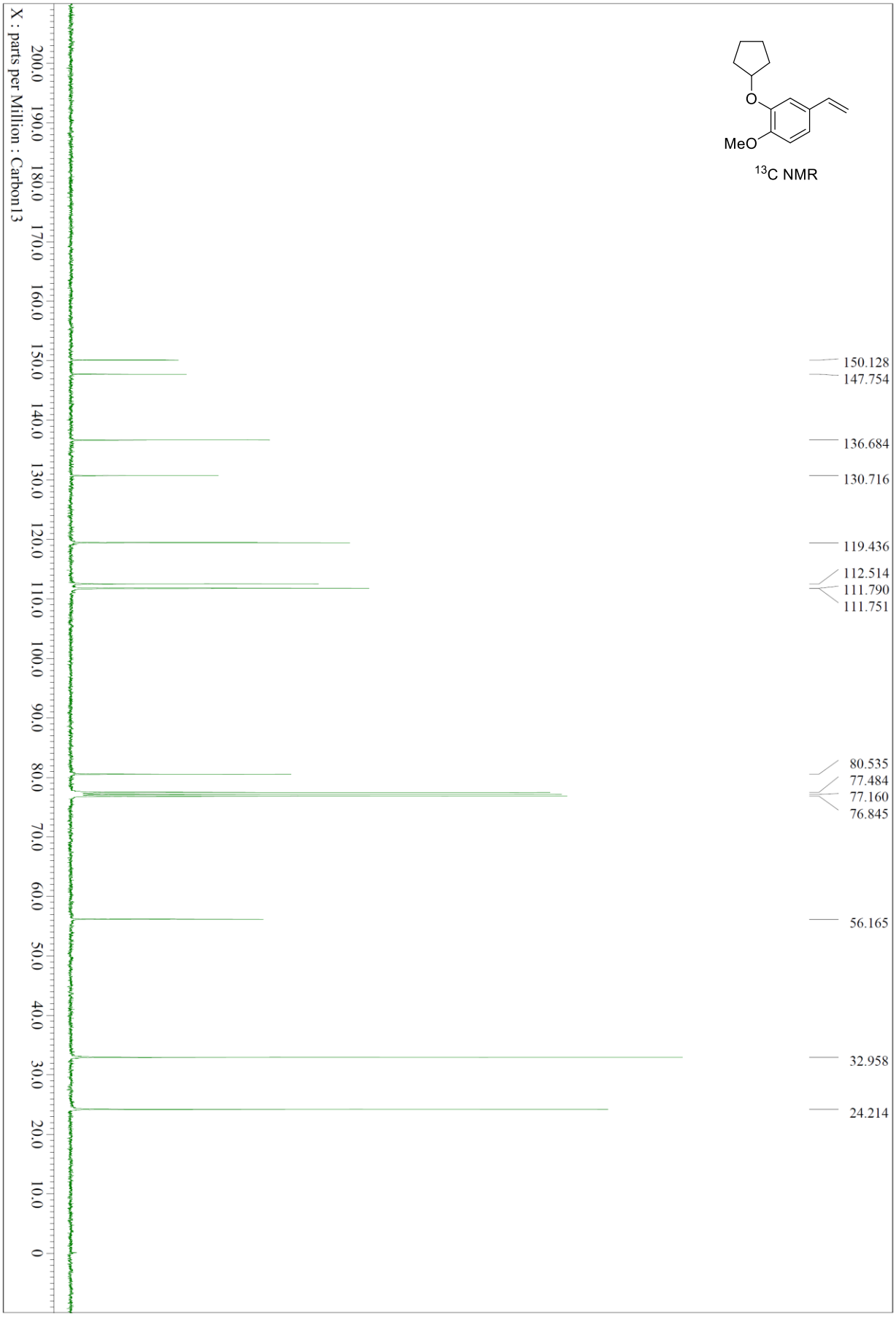
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40.0
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0
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MeO
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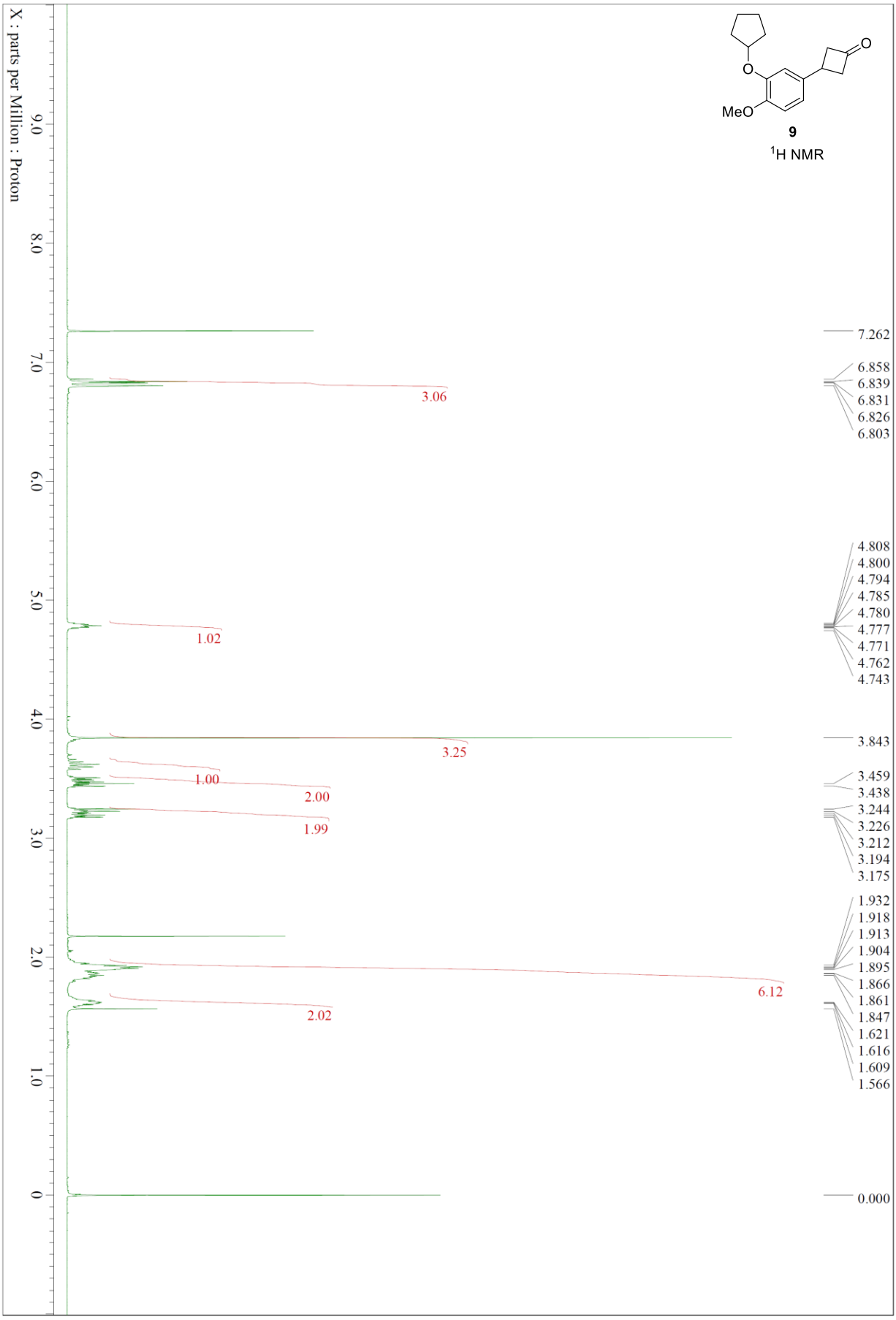
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4.780
4.777
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3.438
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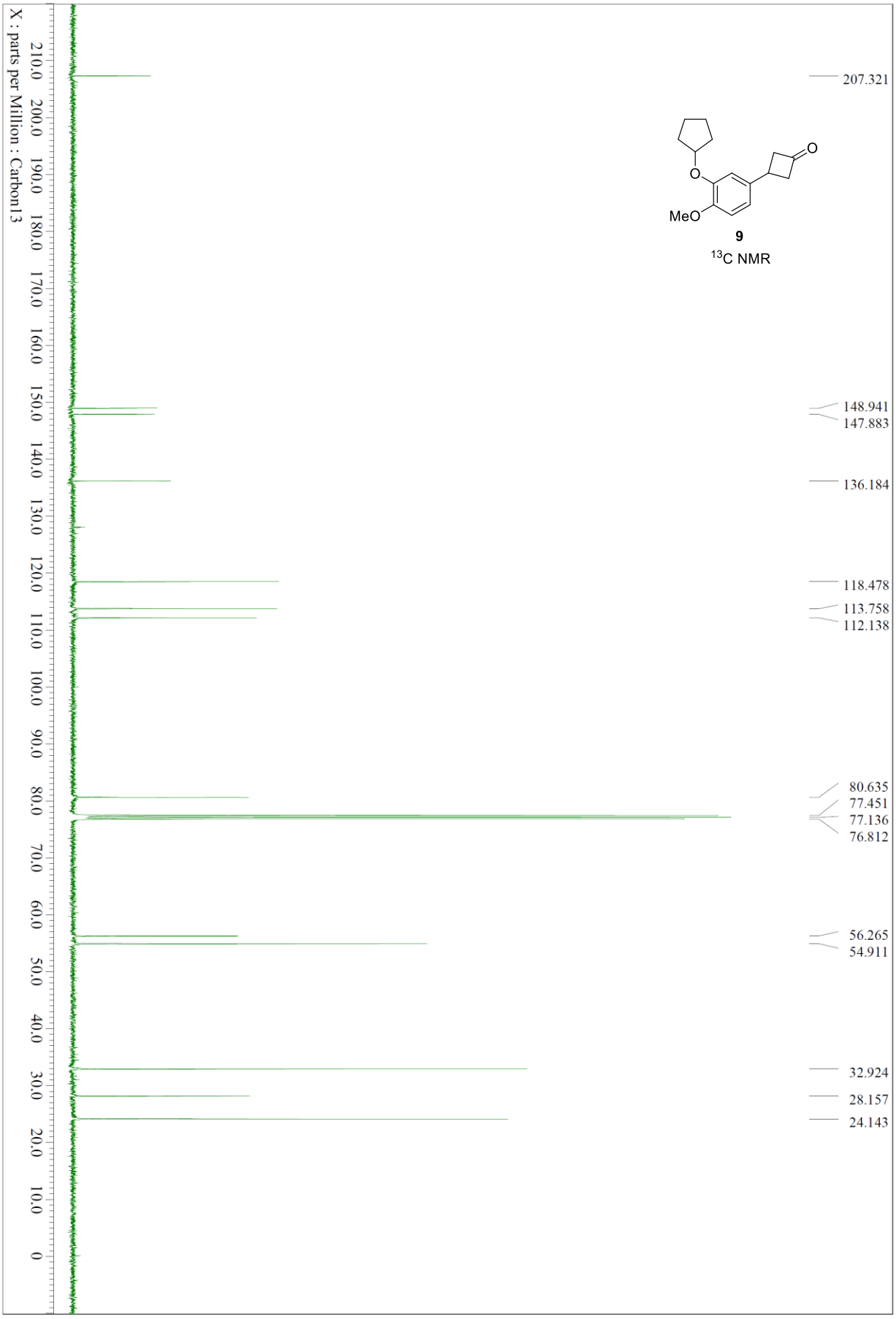
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60.0
50.0
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20.0
10.0
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147.883
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118.478
113.758
112.138
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76.812
56.265
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24.143
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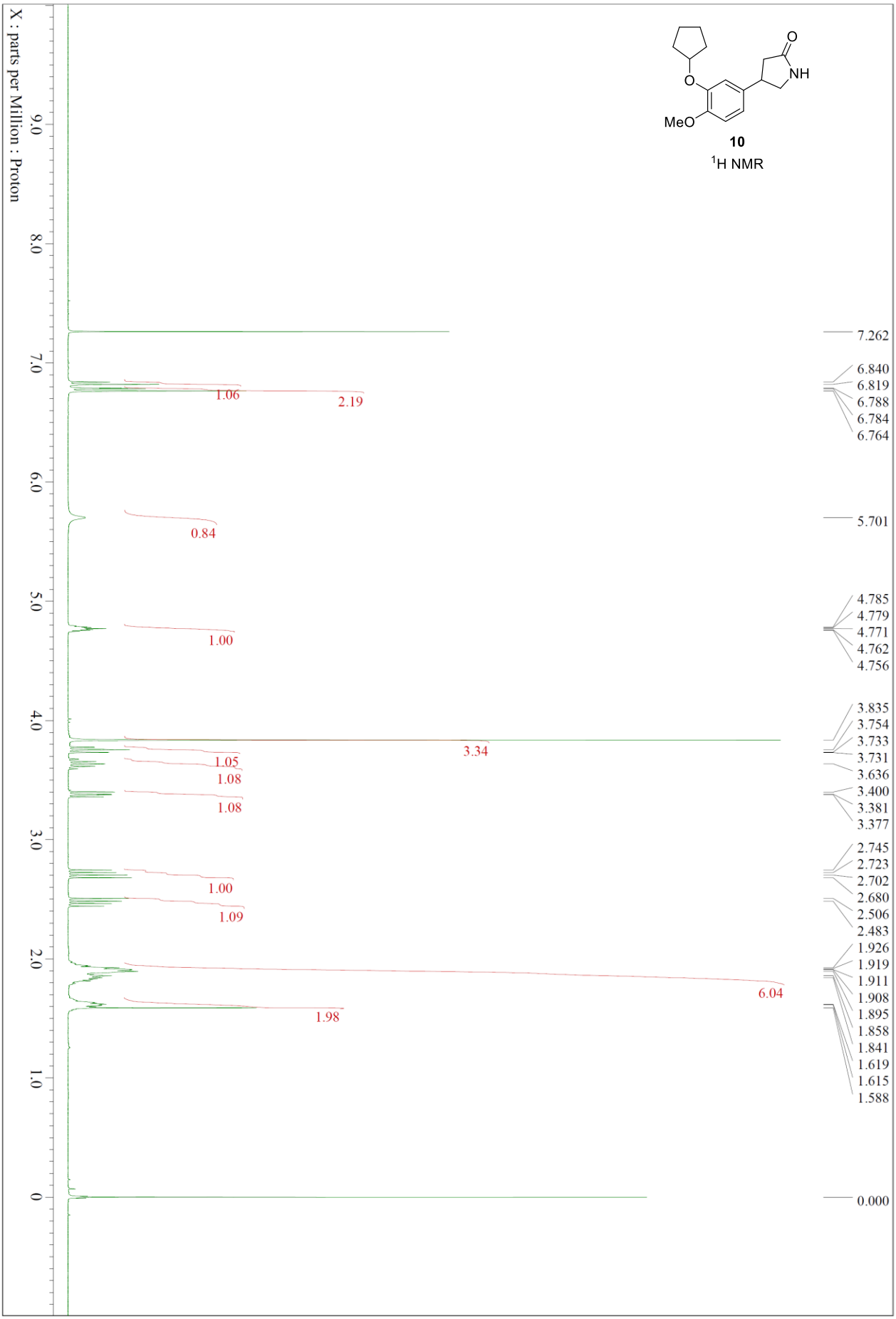
O
MeO
9
13C NMR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MeO
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4.779
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3.754
3.733
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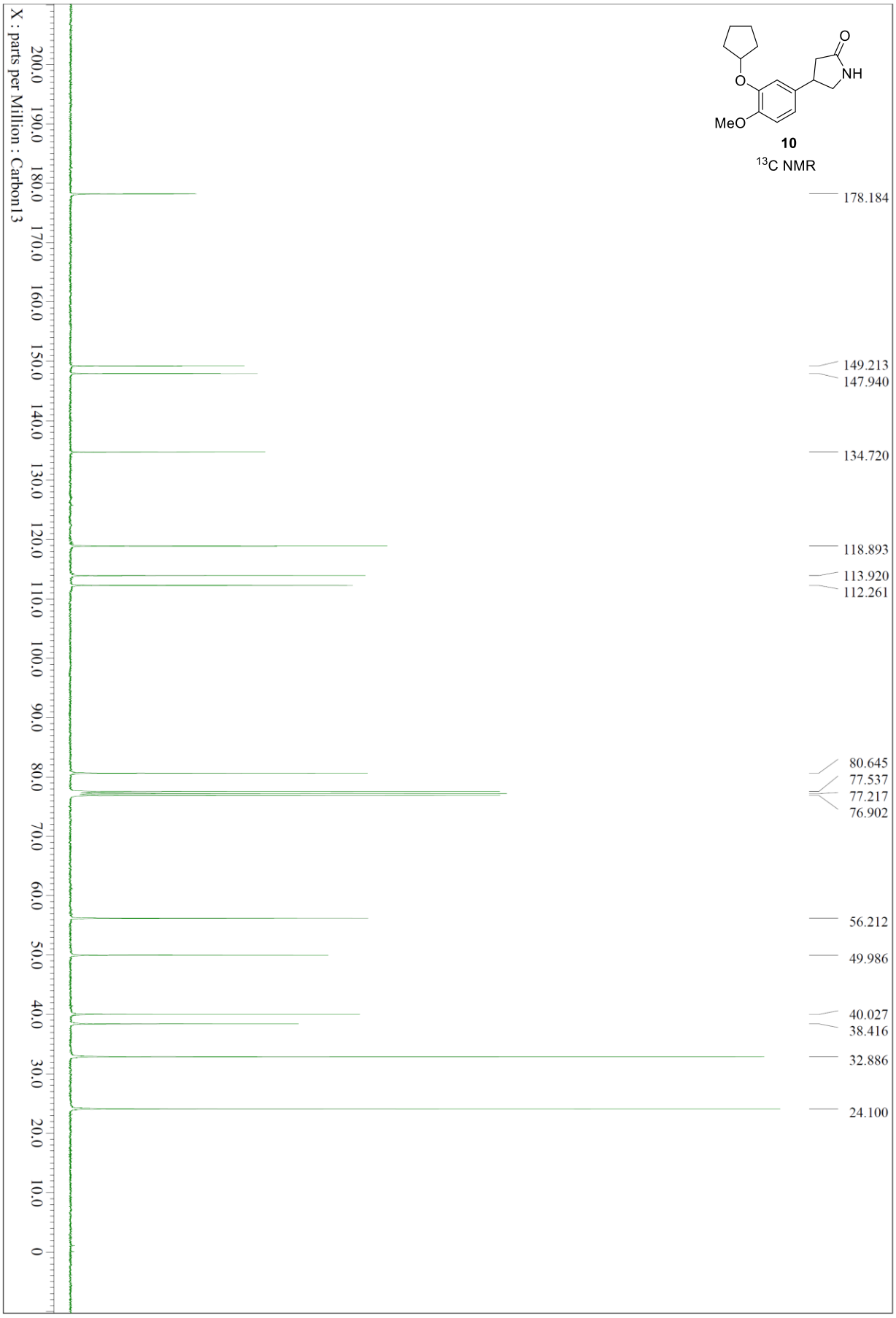
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MeO
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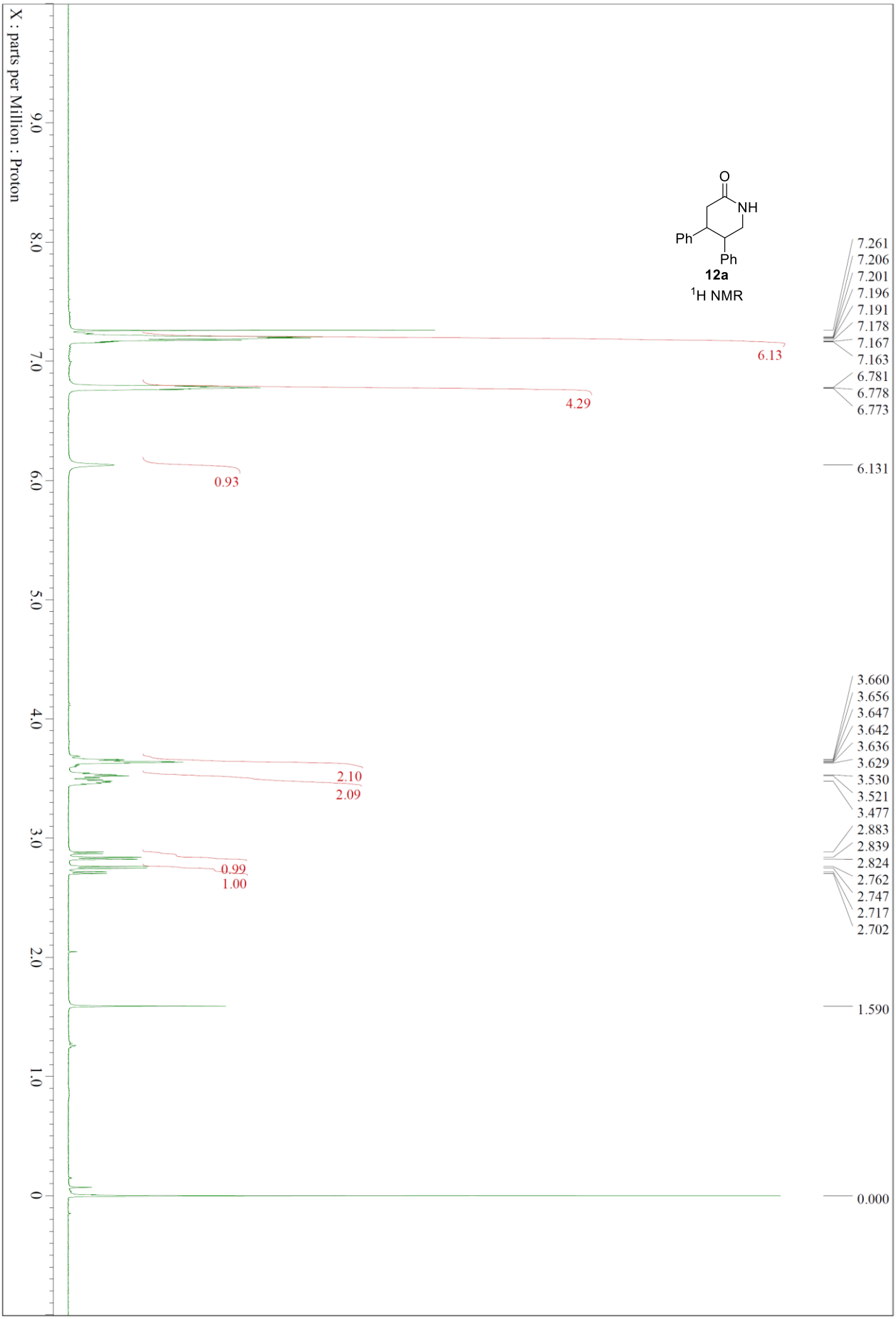
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Ph
Ph
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1H NMR
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2.10
2.09
0.99
1.00
7.261
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7.201
7.196
7.191
7.178
7.167
7.163
6.781
6.778
6.773
6.131
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3.656
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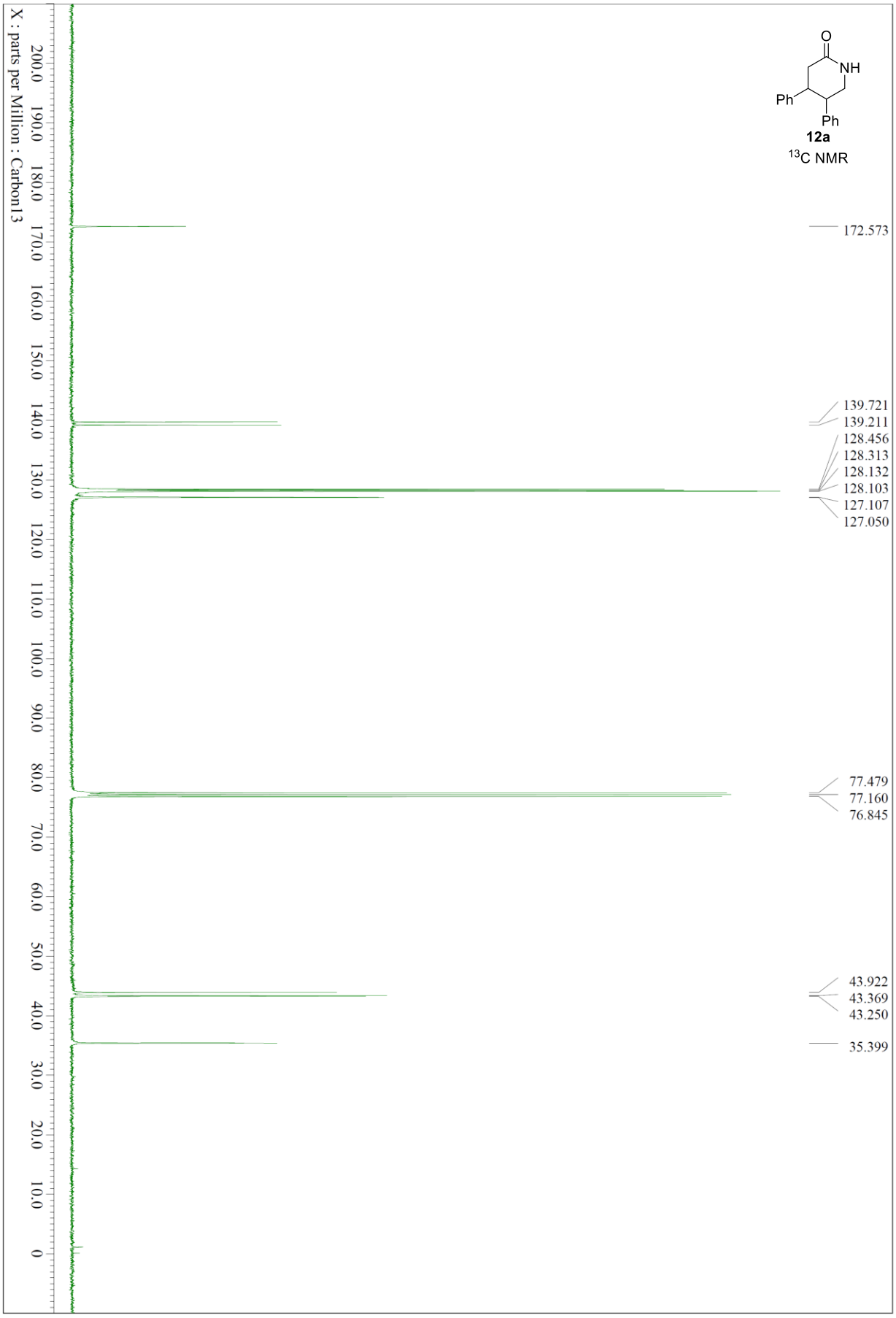
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Ph
Ph
12a
13C NMR
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139.721
139.211
128.456
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127.050
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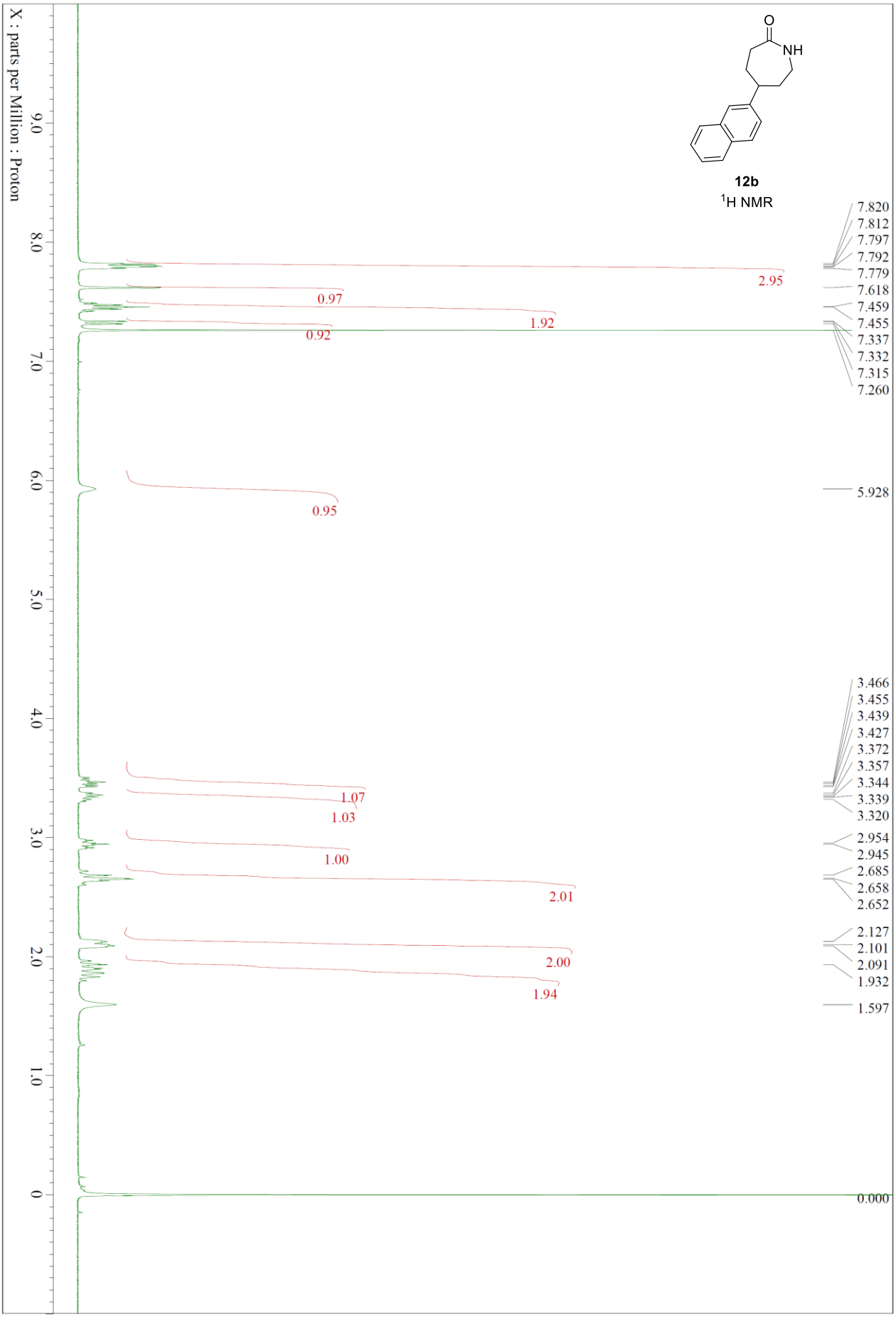
35.399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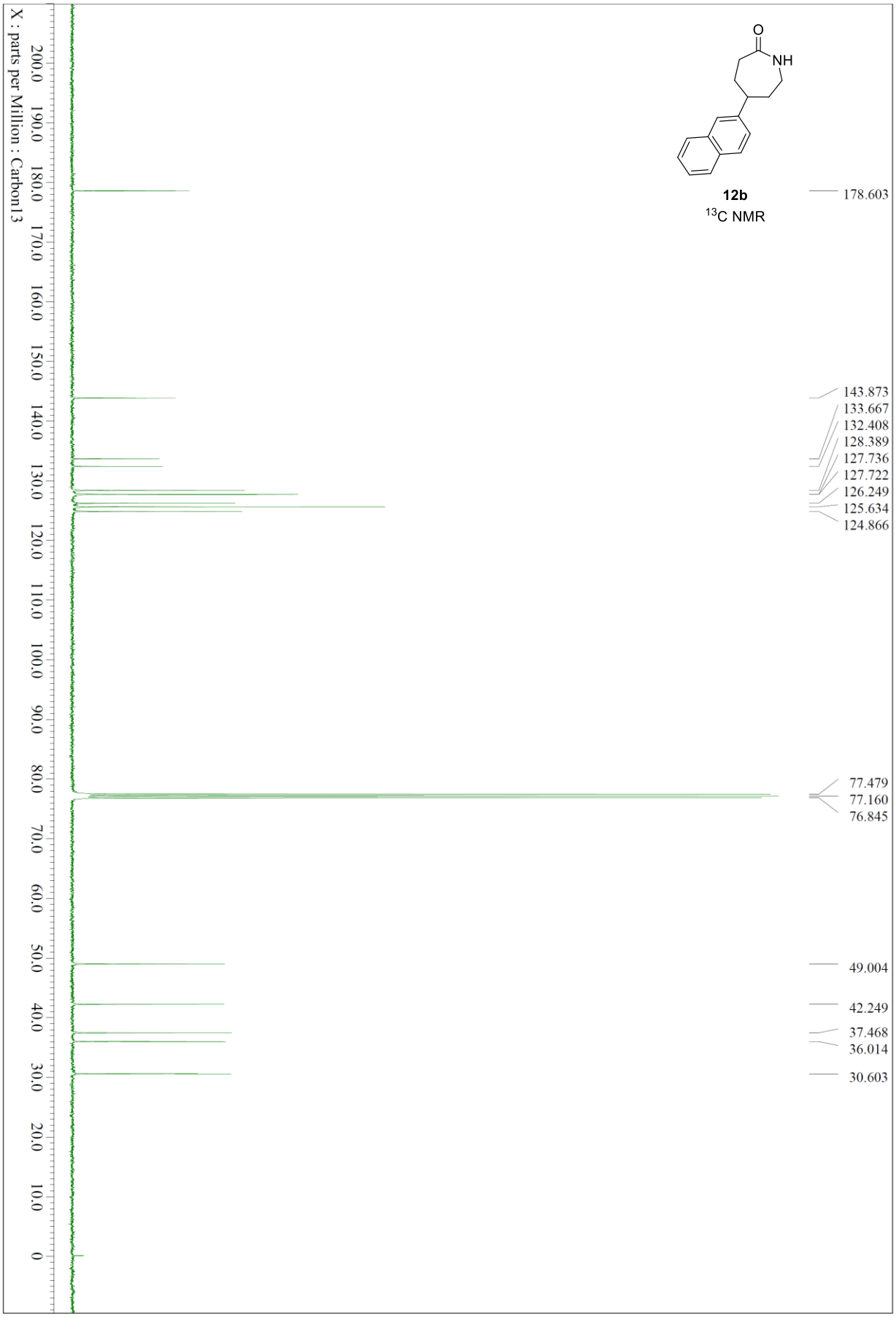
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0
O
NH
12b
13C NMR
178.603
143.873
133.667
132.408
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127.736
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126.249
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42.249
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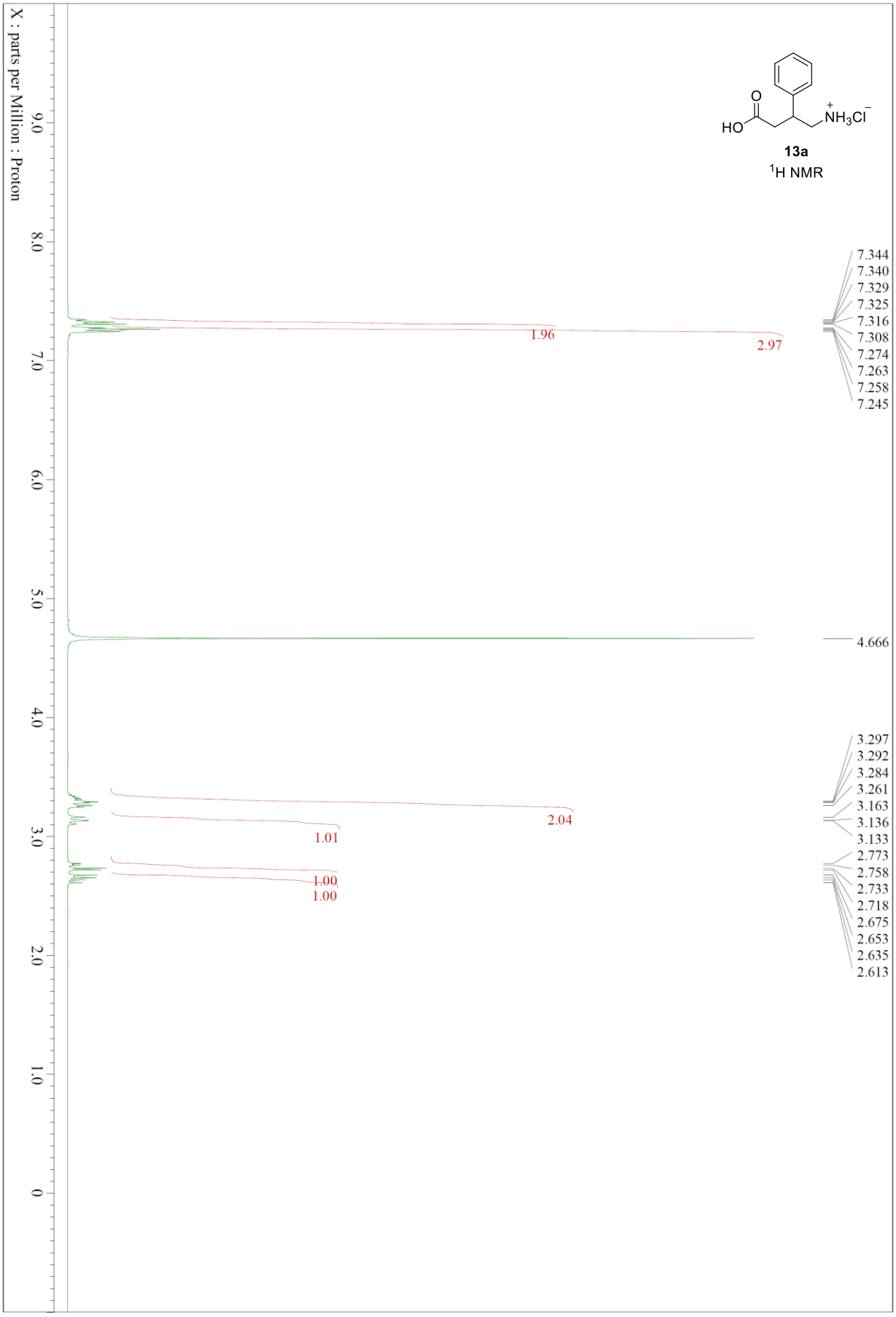
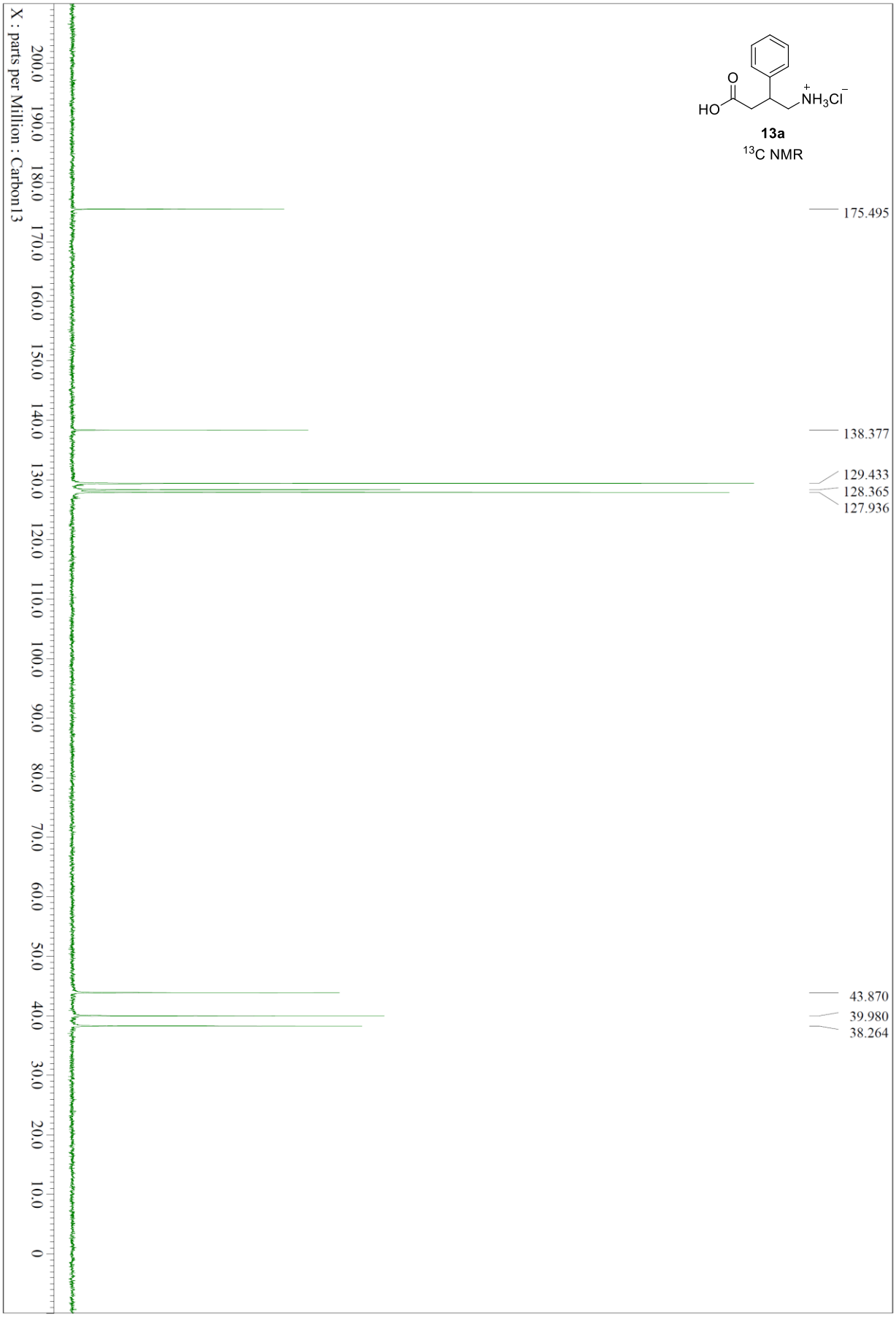
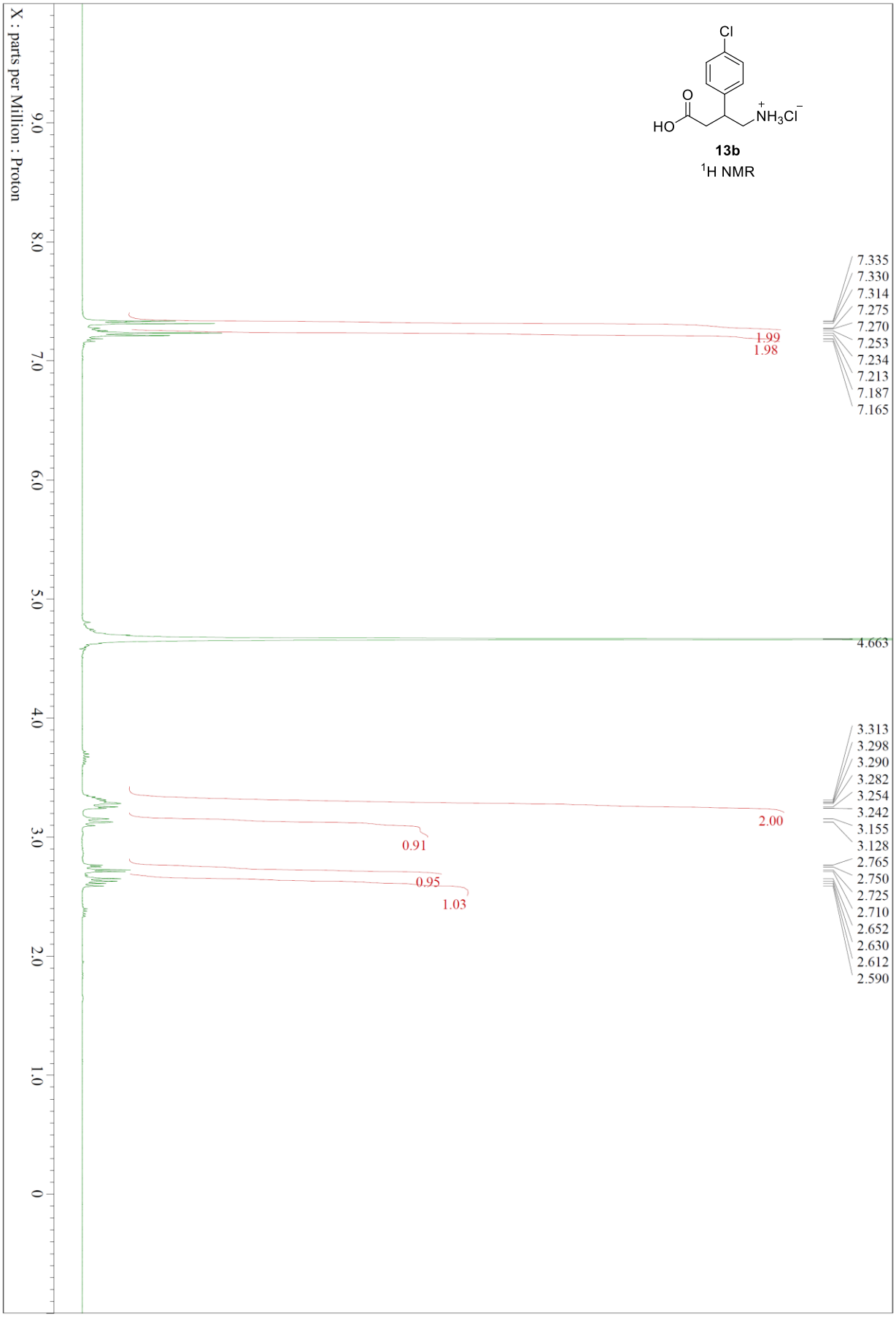
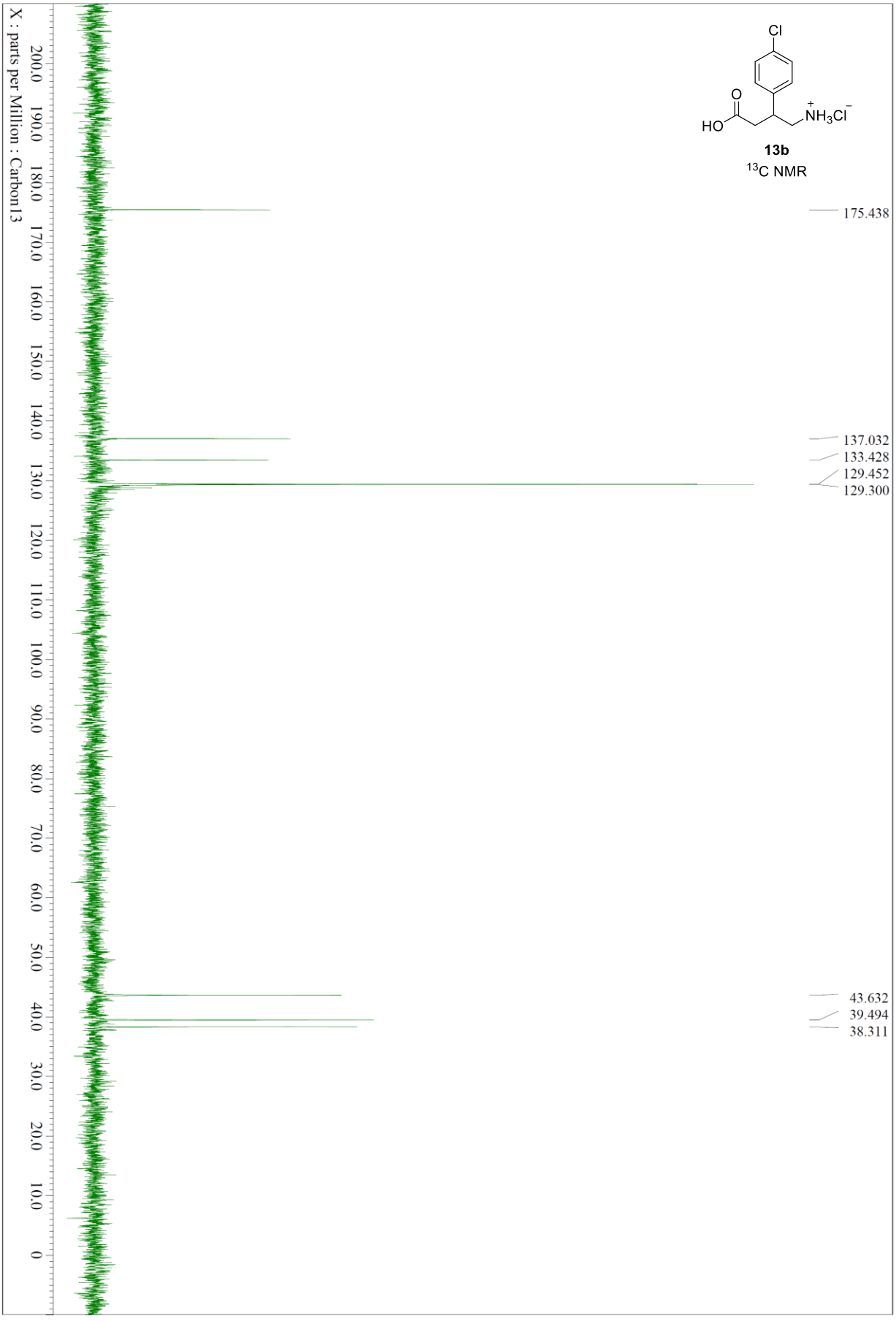
36.014
30.603


X : parts per Million : Proton
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
HO
O
+
NH3Cl−
13a
1H NMR
7.344
7.340
7.329
7.325
7.316
7.308
7.274
7.263
7.258
7.245
1.96
2.97
4.666
3.297
3.292
3.284
3.261
3.163
3.136
3.133
2.04
1.01
1.00
1.00
2.773
2.758
2.733
2.718
2.675
2.653
2.635
2.613


13a
13C NMR
175.495
138.377
129.433
128.365
127.936
43.870
39.980
38.264
X : parts per Million : Carbon13
200.0
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0


X : parts per Million : Proton
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
Cl
O
HO
+
NH3Cl−
13b
1H NMR
7.335
7.330
7.314
7.275
7.270
7.253
7.234
7.213
7.187
7.165
1.99
1.98
4.663
3.313
3.298
3.290
3.282
3.254
3.242
3.155
3.128
2.765
2.750
2.725
2.710
2.652
2.630
2.612
2.590
2.00
0.91
0.95
1.03


Cl
O
HO
+
NH3Cl−
13b
13C NMR
175.438
137.032
133.428
129.452
129.300
43.632
39.494
38.311
X : parts per Million : Carbon13
200.0
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0